SECTION 5

TOXICOLOGICAL PROFILE SUMMARIES FOR TARGET ANALYTES

5.1 INTRODUCTION

This section presents toxicological profile summaries for the target analytes in the same order in which they are listed in Table 1-1. Toxicity data were collected for the target analytes from a variety of sources. Major sources used were IRIS, HSDB, ATSDR Toxicological Profiles, the Office of Pesticide Programs (OPP) toxicological database, and recent toxicological reviews. The EPA risk values discussed in this section were used along with exposure data (e.g., meal size and fish contaminant concentration) to calculate the fish consumption limits provided in Section 4. Primary literature searches and reviews were **not** conducted for the development of this section, due to time and resource constraints.

EPA evaluates dose-response data for chemicals of environmental concern on an ongoing basis. However, new toxicological data are continually being generated. Consequently, there may be recent information that is not yet incorporated into the EPA risk values. This may be particularly relevant for developmental toxicity, which is the subject of much current research. The toxicological summaries provide the reader with information that can be used to calculate alternative health-based risk values and fish consumption limits. The methods for carrying this out are described in Sections 2 and 3.

Risk values are also provided in the individual profiles, accompanied by a discussion of a number of toxicity studies for each target analyte, which yield various dose-response results. These give some indication of the variability in the types of effects and doses at which various effects were observed. Although EPA has developed guidelines for study selection, it is clear that for many chemicals a number of study results could be used to estimate exposure limits. The reader is urged to review the information presented, particularly the studies of chemicals of interest in their areas, so that they may choose the optimal health endpoints from among those discussed in this document (e.g., carcinogenic toxicity, chronic exposure toxicity) or develop their own risk values, based upon their review of the information.

5.1.1 Categories of Information Provided for Target Analytes

Specific types of information were sought for all target analytes to address health and risk concerns for carcinogenic, developmental, and chronic exposure (noncar-

cinogenic) effects. These include pharmacokinetics, acute and chronic toxicity, developmental toxicity, mutagenicity, carcinogenicity, special susceptibilities, interactive effects, and critical data gaps. The categories of information provided for each target analyte are listed in Table 5-1. Although the same types of information were sought for all analytes, the information presented for the contaminants varies, depending on the types of data available. Many of the analytes listed have been recognized as environmental contaminants for a number of years and have a fairly comprehensive toxicological database. Others have been introduced into the environment relatively recently; consequently, only limited information is available on these chemicals.

When a substantial amount of information was available on a contaminant, the information included in the discussions focused on areas relevant to the toxicities under evaluation. For example, a significant amount of pharmacokinetic data is available for some chemicals in the ATSDR Toxicological Profiles. In this document, most information was briefly synopsized; however, detailed information on human milk bioconcentration was included for developmental toxicants if lactational exposure was of concern. In addition, when the toxicological data indicated that a particular type of information, not reported, was required for full exploration of relevant toxic effects, additional information was identified in the Data Gaps Section (e.g., the interaction of DDT with pharmaceutical efficacy arising from DDT-induced increases in levels of microsomal enzymes).

The information collected is categorized by the temporal nature of the exposure (e.g., acute, chronic). These groupings are most applicable to the standard risk assessment methods that were employed to calculate risk values. The temporal groupings and methods of evaluating dose-response data are briefly discussed in Section 2, with a description of uncertainties and assumptions associated with dose-response evaluation.

5.1.1.1 Pharmacokinetics—

A brief summary of the pharmacokinetic data is presented for many chemicals. The information, obtained primarily from ATSDR toxicological profiles, was included if it had a bearing on the development of fish consumption limits or would be useful to the reader in evaluating the toxicological characteristics of a chemical. For more detailed information on pharmacokinetics, the reader is referred to the ATSDR profiles and the primary literature.

For most chemicals there was not sufficient quantitative information, such as absorption, uptake, distribution, metabolism, excretion, and metabolite toxicity, in the data reviewed to recommend modifications in exposure to yield an altered internal dose. Some chemicals contained in the IRIS database have risk values that have incorporated pharmacokinetic considerations. If additional information relevant to quantitative risk assessment becomes available, it will be included in future versions of this guidance document.

Table 5-1. Health and Toxicological Data Reviewed for Target Analytes

Category	Specific Information
Background	Chemical structure/group Use and occurrence
Pharmacokinetics	Target tissues Absorption Deposition-bioaccumulation potential/half-life/body burden Metabolism Excretion Susceptible subgroups
Acute toxicity	Quantitation Susceptible subgroups
Chronic toxicity	Organ systems Animal studies-quantitation Human studies-quantitation Other studies-quantitation Database quality Susceptible subgroups Current risk values
Developmental toxicity	Organ systems Animal studies-quantitation Human studies-quantitation Other studies-quantitation Database quality Susceptible subgroups Current risk values
Mutagenicity	Type Quantitation Source Database quality
Carcinogenicity	Organ systems Animal studies-quantitation Human studies-quantitation Other studies-quantitation Database quality Outstanding issues
Special susceptibilities	Subgroups of concern
Interactive effects	Qualitative Quantitative MIXTOX results
Critical data gaps	Description
Summary of EPA risk values	Cancer slope factor and reference dose

5.1.1.2 Acute Toxicity—

Very little acute exposure toxicity data were located that could have a quantitative bearing on the development of fish consumption limits. A qualitative description of acute effects is included. The minimum estimated lethal dose to humans and a brief discussion of the acute effects are included if the data were available. In addition, the Minimum Risk Levels developed by ATSDR are included when available. They provide estimates of the levels of exposure for a chemical (e.g., toxaphene) at which minimum risk is expected to occur (ATSDR, 1990b). In addition, Appendix C contains a discussion of general class information for two major categories of chemicals, the organochlorines and organophosphates, which constitute 14 of the 25 target analytes.

5.1.1.3 Chronic Toxicity—

Under the chronic exposure heading, significant effects associated with long-term exposure are listed. These include effects on the major organs and systems: the liver, kidney, gastrointestinal, cardiovascular, and reproductive systems. The chronic exposure data for each analyte includes a description of an RfD listed in IRIS or obtained from other sources and the critical study serving as the basis for that RfD, including the species tested, duration of the study, and critical effect noted. Information is provided on any unusual aspects of the study or RfD (e.g., if the study is old or has very few subjects or if the confidence in the RfD is listed as “low”).

Data are also provided on effects observed in recent dose-response studies or effects that were not the subject of the IRIS RfD critical study. This was done to provide a more comprehensive picture of the overall toxicological nature of the chemicals than could be obtained from reviewing the RfD critical study alone. For most analytes, the information is primarily a qualitative description of effects. For chemicals that have significant new toxicological data available, details are provided on NOAELs, LOAELs, some study characteristics, and the usual categories of uncertainty and modifying factors that should be considered for significant studies. These are provided to give readers the option of developing exposure limits as they deem necessary.

5.1.1.4 Developmental Toxicity—

Developmental toxicity data were obtained for each target analyte (dioxin information will be provided when the EPA dioxin reassessment is complete in 1998). Section 2.3.2.3 contains general information on developmental toxicity, including definitions, methods for calculating exposure limits, and special issues related to developmental toxicity. The data and methods information are provided to give readers the option of developing exposure limits based on developmental effects, as they deem necessary.

For many chemicals, information is provided on the tendency of the chemical to accumulate in body tissue. Many of the target analytes bioaccumulate and/or preferentially seek fatty tissues. When such accumulation occurs, exposure occurring prior to pregnancy can contribute to the overall maternal body burden and result in exposure to the developing fetus. Any body burden may result in exposure, but lipid-seeking chemicals, such as organochlorines, are often rapidly mobilized at the onset of pregnancy and may result in elevated contaminant exposure to the developing fetus. As a result, it may be necessary to reduce the exposure of females of reproductive age in order to reduce their overall body burden. If a female has been exposed to endrin, even if exposure is reduced during pregnancy, the outcome of that pregnancy may be affected, depending on the timing and extent of prior exposure. This is noted for bioaccumulative analytes in the individual toxicological profiles.

5.1.1.5 Mutagenicity—

Although there were many reported mutagenicity bioassays for target analytes, little in vivo mutagenicity dose-response data were located. In vivo studies are recommended by EPA for risk assessments of suspected mutagens. A brief summary of the results of the mutagenicity assays for the analytes is provided. There are numerous studies available for some of the contaminants; consequently, all results could not be feasibly listed. To provide a more concise overview of the results of greatest concern, the nature of the positive studies is given. The direction of the majority of results is also given (e.g., primarily positive, negative, or mixed).

5.1.1.6 Carcinogenicity—

Cancer slope factors and descriptive data were obtained primarily from IRIS, HEAST, and OPP. Preference was given to IRIS values; however, when IRIS values were not available, values developed by Agency program offices (e.g., OPP) are provided. The program office values have not necessarily undergone the extensive interagency review required for inclusion in the IRIS database, although many have been reviewed by scientists within and outside of EPA.

There are often insufficient studies to evaluate the carcinogenicity of a chemical. EPA has recognized this and formalized the lack of data as classification D: “not classifiable as to human carcinogenicity” in EPA’s current cancer weight of evidence scheme (U.S. EPA, 1986a). Many target analytes fall into this category; for others, no data were found in the sources consulted regarding their carcinogenicity. For chemicals with insufficient or no data on carcinogenicity in the databases consulted, the text under the “Carcinogenicity” heading states that: “insufficient information is available to determine the carcinogenic status of the chemical.” This statement is used for chemicals lacking a cancer slope factor unless an Agency-wide review has determined that there is evidence that the chemical is **not** carcinogenic (i.e., an E classification as provided in IRIS, 1997). For a complete description of EPA’s current weight-of-evidence classification scheme, see EPA’s *Guidelines for Carcinogenic Risk Assessment* (U.S. EPA,

1986a). EPA's proposed cancer guidelines have replaced this weight-of-evidence classification scheme with a narrative with descriptors in three categories: "known/likely," "cannot be determined," or "not likely" (U.S. EPA, 1996d).

5.1.1.7 Special Susceptibilities—

Toxicity data often indicate that some groups of individuals may be at greater risk from exposure to chemicals or chemical groups. For example, a chemical that causes a specific type of organ toxicity will usually pose a greater risk to individuals who have diseases of that organ system (e.g., immunotoxicity poses a greater risk to those with immunosuppression or with immature immune systems). Persons with some genetic diseases (e.g., enzyme disorders), nutritional deficiencies, and metabolic disorders may also be at greater risk due to exposure to some chemicals. Qualitative data on special susceptibilities are provided for many of the target analytes. In addition, information is provided on susceptibilities of special concern for groups of chemicals (e.g., organophosphates) in Appendix C. However, there are no quantitative data on subgroup susceptibilities for most chemicals that would enable the risk assessor to modify risk values.

The RfDs are designed to take into account the most susceptible individuals, and RfDs often incorporate an uncertainty factor to account for variability within the human species. The U.S. Public Health Service has provided specific nonquantitative guidance regarding susceptible subgroups in the ATSDR Toxicity Profiles; it is included in the individual toxicological profiles in Sections 5.2 through 5.8. In addition, there are some general caveats regarding special susceptibilities that should be considered. Exposure to many types of toxicants poses higher risks to children due to their immaturity:

> embryos, fetuses, and neonates up to age 2 to 3 months may be at increased risk of adverse effects . . . because their enzyme detoxification systems are immature
>
> and
>
> Infants and children are especially susceptible to immunosuppression because their immune systems do not reach maturity until 10 to 12 years of age (ATSDR, 1990b).

ATSDR has also cautioned that:

> the elderly with declining organ function and the youngest of the population with immature and developing organs will generally be more vulnerable to toxic substances than healthy adults (ATSDR, 1993a).

5.1.1.8 Interactive Effects—

Data on interactive effects were located for many, but not all, of the target analytes. Most data on interactive effects were obtained from ATSDR Toxicological Profiles. Often the data indicate that certain classes of chemicals may be of concern. For example, most organochlorines induce the mixed function oxidase system. These chemicals may lead to unanticipated and exaggerated or diminished effects arising from simultaneous exposure to other chemicals that rely on the same metabolic system. In some cases this leads to potentiation (increased toxicity) and in others it hastens the process of detoxification.

The MIXTOX database, developed by EPA, was also used to obtain information on interactive effects (MIXTOX, 1992). The database provides a very brief summary of results of studies on combinations of chemicals. Most interactions are reported as "potentiation," "inhibition" or "antagonism" (decreased toxicity), "no apparent influence," or "additive." The interactions that differ from additive or no apparent influence are reported because it is assumed, in the absence of contrary information, that the toxicity of mixtures of chemicals will be additive for the same target tissue (see Section 2.3). The interactive terminology used in MIXTOX is used in this document.

5.1.1.9 Critical Data Gaps—

Data gaps noted in IRIS files, the OPP toxicological database, RfD summaries, and the ATSDR Toxicological Profiles are listed. In addition, data gaps that have been identified from a review of the studies are listed, along with the reasons that additional data are considered necessary. For example, if very limited study data are available on developmental toxicity, but developmental toxicity is indicated in the database, developmental studies are listed as a data gap.

5.1.1.10 Summary of EPA Levels of Concern—

The EPA risk values (RfDs and cancer slope factor) discussed in each section and used in the development of fish consumption limits are summarized in Table 3-1.

5.1.1.11 Major Sources—

At the end of each target analyte file is a list of the major sources of information consulted. Major sources are those that have been cited more than once. Within the text of each target analyte file, all information is provided with citations.

The IRIS files were consulted in early 1997 for cancer slope factor, chronic exposure RfDs, and additional study data. ATSDR Toxicological Profiles were also consulted when available. The profiles have extensive toxicity, pharmacokinetic, and epidemiological data reviews and provide estimated Minimum Risk Levels, which are analogous to RfDs in that they are "estimates of levels posing minimal risk to humans" (ATSDR, 1992a). They are based upon risk assessment methods similar to those used by EPA. The ATSDR documents were particularly useful

because they provide detailed information and because many provide extensive discussions of developmental effects as well as some MRLs for these effects. Some ATSDR profiles cited are draft documents; however, the profiles underwent extensive review within and outside of the U.S. Public Health Service before they were released as the draft bound copies that are cited in this work.

5.1.1.12 Statement Regarding Uncertainty—

There are always significant uncertainties associated with estimating health risks and safe exposure levels for human populations. Although these are discussed in Section 2, their importance warrants their mention in this section also. The risk values provided for each chemical in this section are based on human or animal studies that evaluated either a small subset of the human population or an entirely different species. In either case, we can only **estimate** the relevance of the study results to humans. Although a quantitative methodology is used to extrapolate from various types of studies to the general human population, there is considerable uncertainty in the estimated relationship between study populations and the human population.

The use of uncertainty factors and upper bound cancer risk estimates provides a margin of safety to account for some aspects of uncertainty in the extrapolation. However, our knowledge of response variability in the human population is very limited. The variations in response, which are engendered by age, sex, genetic heterogeneity, and preexisting disease states, may be considerable. Consequently, although current approaches to assessing risk involve estimating the upper bound values for deriving exposure or risk and are intended to be protective rather than predictive, the reader is urged to carefully review the information provided in this section on data gaps and uncertainties.

It is important to describe the uncertainties and assumptions when recommending fish consumption limits. With respect to toxicity, these include both uncertainties associated with specific chemicals and uncertainties and assumptions associated with the dose-response evaluation process (described in Section 2). In some cases, a variety of dose-response data will enable the reader to provide a quantitative estimation of the range of potential risk values that could be used to calculate exposure and fish consumption limits. A description of data gaps may also be useful to the risk manager in determining the best course of action. For chemicals having few data, only a qualitative description may be possible.

5.1.2 Abbreviations Used and Scientific Notation

The abbreviations NOEL, NOAEL, LEL, LOEL, and LOAEL are used in this document as they appear in the original sources. Although they have specific meanings (see the Glossary), NOEL-NOAEL and LEL-LOEL-LOAEL are sometimes used interchangeably. Since it was not possible to determine the intent of the authors of the source documents, the terms were used as they appeared in those documents.

The glossary contains a description of additional terms and abbreviations used in this section.

Scientific notation is used where the values are less than 0.001 unless it would introduce confusion to the text (e.g., when presenting a range, the same format is used for both values in the range). In the summaries of risk values, all noncancer risk values are presented in scientific notation to facilitate comparison across health endpoints.

5.2 METALS

5.2.1 Arsenic

5.2.1.1 Background—

Arsenic is a naturally occurring element in the earth's crust that is usually found combined with other elements. Arsenic combined with elements such as oxygen, chlorine, and sulfur is referred to as inorganic arsenic; arsenic combined with carbon and hydrogen is referred to as organic arsenic. In this toxicological profile, arsenic refers to inorganic arsenic and its associated compounds. Organic arsenic compounds, such as arsenobetaine (an organic arsenic compound found in the edible parts of fish and shellfish) are not discussed, since these compounds are considered to be relatively nontoxic and not a threat to human health (ATSDR, 1993e).

5.2.1.2 Pharmacokinetics—

Pharmacokinetic studies show that water-soluble arsenic are well-absorbed across the gastrointestinal tract. They appear to be transported throughout the body; analysis of tissues taken at autopsy from people who were exposed to arsenic found arsenic present in all tissues of the body. The arsenic levels in hair and nails were the highest, with somewhat lower levels in internal organs (ATSDR, 1993e).

The metabolism of arsenic consists mainly of a reduction reaction, which converts pentavalent arsenic to trivalent arsenic, and methylation reactions, which convert arsenite to monomethylarsonic acid and dimethylarsenic acid. The primary excretion route for arsenic and metabolitis is in the urine, with human studies showing that 45 to 85 percent is excreted in the urine within 1 to 3 days. Very little is excreted in the feces (ATSDR, 1993e).

5.2.1.3 Acute Toxicity—

Arsenicals have been recognized as a human poison since ancient times, and large doses, approximately 600 µg/kg/d or higher, taken orally have resulted in death. Oral exposure to lower levels of arsenic has resulted in effects on the gastrointestinal system (nausea, vomiting); central nervous system (headaches, weakness, delirium); cardiovascular system (hypotension, shock); and the liver, kidney, and blood (anemia, leukopenia). Because significant information is available on the acute effects of arsenic poisoning in humans, few animal studies have been carried out. The limited available data have shown arsenic to have low to moderate acute toxicity to animals. This is based on data showing the LD_{50}s for arsenic to range between 50 and 5,000 mg/kg (ATSDR, 1993e).

5.2.1.4 Chronic Toxicity—

The primary effects noted in humans from chronic exposure to arsenic are effects on the skin. Oral exposure has resulted in a pattern of skin changes that include

the formation of warts or corns on the palms and soles, along with areas of darkened skin on the face, neck, and back. Blackfoot disease, a disease characterized by a progressive loss of circulation in the hands and feet, leading ultimately to necrosis and gangrene, is associated with arsenic (ATSDR, 1993e). Other effects noted from chronic oral exposure include peripheral neuropathy, cardiovascular disorders, and liver and kidney disorders.

IRIS provides an RfD for inorganic arsenic of 3.0×10^{-4} mg/kg/d, based on a NOAEL (adjusted to include arsenic exposure from food) of 0.0008 mg/kg/d and an uncertainty factor of 3. This was based on two studies that showed that the prevalence of blackfoot disease increased with both age and dose for individuals exposed to high levels of arsenic in drinking water. This same population also displayed a greater incidence of hyperpigmentation and skin lesions. Other human studies support these findings, with several studies noting an increase in skin lesions from chronic exposure to arsenic through the drinking water. An uncertainty factor of 3 was used to account for both the lack of data to preclude reproductive toxicity as a critical effect and for uncertainty as to whether the NOAEL of the critical studies accounts for all sensitive individuals (IRIS, 1997). ATSDR has calculated a chronic oral MRL that is equal to the RfD listed in IRIS (ATSDR, 1993e).

EPA has medium confidence in the studies on which the RfD was based and in the RfD. The key studies were extensive epidemiologic reports that examined effects in a large number of people. However, doses were not well-characterized, other contaminants were present, and potential exposure from food or other sources was not examined. The supporting studies suffer from other limitations, primarily the small populations studied. However, the general database on arsenic does support the findings in the key studies; this was the basis for EPA's "medium confidence" ranking of the RfD (IRIS, 1997).

5.2.1.5 Developmental Toxicity—

Limited information is available on the developmental effects of arsenic in humans. No overall association between arsenic in drinking water and congenital heart defects was detected in an epidemiological study, although an association with one specific lesion (coarctation of the aorta) was noted. However, due to the small number of cases, this association might be due to random variation. In another study, a marginal association (not statistically significant) was found between detectable levels of arsenic in drinking water and spontaneous abortions. However, a similar association was found for a number of compounds, which indicates that the association could be random or due to other risk factors (ATSDR, 1993e).

Minimal or no effects on fetal development have been observed in studies on chronic oral exposure of pregnant rats or mice to low levels of arsenic in drinking water. Malformations were produced in 15-day hamster fetuses via intravenous injections of arsenic into pregnant dams on day 8 of gestation, while another study

reported that very high single oral doses of arsenic were necessary to cause prenatal fetal toxicity (IRIS, 1997).

5.2.1.6 Mutagenicity—

In vivo studies of arsenic have shown mixed results. Some studies on chromosomal aberrations and sister chromatid exchange in human lymphocytes reported positive results, while others were negative. One study in mouse bone marrow cells reported an increase in micronuclei, while another did not report an increase in chromosomal breaks and exchanges (ATSDR, 1993e). In vitro studies have also reported both positive and negative results. Arsenic was negative in the bacterial colorimetric assay: SAS Chromotest (HSDB, 1997), and positive for reverse mutations in bacteria, morphological transformations in Syrian hamster embryo cells, and chromosomal aberrations in human leukocytes (ATSDR, 1993e).

5.2.1.7 Carcinogenicity—

There is clear evidence that chronic exposure of humans to inorganic arsenic increases the risk of cancer. Ingestion of arsenic has been associated with an increased risk of nonmelanoma skin cancer, and bladder, liver, and lung cancer. In addition, studies have reported that inhalation of arsenic results in an increased risk of lung cancer (IRIS, 1997).

Animal studies have not associated arsenic exposure, via ingestion, with cancer. All cancer studies in rodents with arsenic have reported negative results; however, the meaning of this nonpositive data is uncertain; the mechanism of action in causing human cancer is not known, and rodents may not be a good model for arsenic-induced carcinogenicity (IRIS, 1997).

EPA has classified inorganic arsenic in Group A—Known Human Carcinogen. This is based on the increased incidence in humans of lung cancer through inhalation exposure and the increased risk of skin, bladder, liver, and lung cancer through drinking water exposure (IRIS, 1997).

To estimate the risks posed by ingestion of arsenic, EPA uses data from Taiwan concerning skin cancer incidence, age, and level of exposure via drinking water. In 37 villages that had obtained drinking water for 45 years from artesian wells with various elevated levels of arsenic, 40,421 individuals were examined for hyperpigmentation, keratosis, skin cancer, and blackfoot disease. The local well waters were analyzed for arsenic, and the age-specific cancer prevalence rates were found to be correlated with both local arsenic concentrations and age (duration of exposure). The oral cancer potency is 1.5 per mg/kg/d (IRIS, 1997).

5.2.1.8 Special Susceptibilities—

ATSDR reported that no studies were located regarding unusual susceptibility of any human subpopulation to arsenic. However, it is possible that some members

of the population might be especially susceptible because of lower than normal methylating capacity. This could result from a dietary deficiency of methyl donors such as choline or methionine or a deficiency of the vitamin coenzymes (folacin, Vitamin B_{12}) involved in transmethylation reactions (ATSDR, 1993e; Rogers, 1995).

5.2.1.9 Interactive Effects—

Arsenic tends to reduce the effects of selenium, and selenium can decrease the effects of arsenic. No clear evidence exists for significant interactions between arsenic and other metals; the existing data do not suggest that arsenic toxicity is likely to be significantly influenced by concomitant exposure to other metals. Suggestive evidence exists that a positive interaction between arsenic and benzo(*a*)pyrene can occur for lung adenocarcinomas in animals. Other studies suggest that chemicals that interfere with the methylation process could increase the toxicity of arsenic (ATSDR, 1993e)

5.2.1.10 Critical Data Gaps—

There is a substantial database on the toxicity of arsenic, both in humans and in animals. However, there are some areas where studies are lacking, such as short-term animal studies to define an acute or intermediate-duration MRL. In addition, epidemiological studies to provide additional support for the threshold dose for arsenic in humans are lacking and would be valuable. Additional studies on developmental and reproductive effects of arsenic would also be useful (ATSDR, 1993e).

5.2.1.11 Summary of EPA Levels of Concern—

Chronic Toxicity	3.0×10^{-4} mg/kg/d
Carcinogenicity	1.5 per mg/kg/d.

5.2.1.12 Major Sources—

ATSDR (1993e), HSDB (1997), IRIS (1997), Rogers (1995).

5.2.2 Cadmium

5.2.2.1 Background—

Cadmium is a heavy metal that is released through a wide variety of industrial and agricultural activities. It accumulates in human and other biological tissue and has been evaluated in both epidemiological and toxicological studies. ATSDR has determined that exposure conditions of most concern are long-term exposures to elevated levels in the diet (ATSDR, 1993a).

The FDA has estimated that cadmium exposure among smokers is approximately 10 µg/d (0.01 mg/d). Passive exposure of nonsmokers may also be a source of

exposure (U.S. FDA, 1993). This should be considered in evaluating the total exposure and risks associated with cadmium.

5.2.2.2 Pharmacokinetics—

Cadmium is not readily absorbed when exposure occurs via ingestion. Most ingested cadmium passes through the GI tract without being absorbed. Studies in humans indicate that approximately 25 percent of cadmium consumed with food was retained in healthy adults after 3 to 5 days; this value fell to 6 percent after 20 days. Absorption may be much higher in iron-deficient individuals. Evaluations of the impact of cadmium complexation indicate that cadmium absorption from food is not dependent upon chemical complexation. However, some populations with high dietary cadmium intakes have elevated blood cadmium levels, and this may be due to the particular forms of cadmium in their food (ATSDR, 1993a).

Cadmium absorption studies in animals indicate that the proportion of an oral dose that is absorbed is lower in animals than in humans. Absorption is elevated during pregnancy, with whole-body retention in mice of 0.2 percent in those that had undergone pregnancy and lactation and 0.08 percent in those that had not. In rats, absorption decreased dramatically over the early lifetime ranging from 12 percent at 2 hours to 0.5 percent at 6 weeks after birth. The placenta may act as a partial barrier to fetal exposure, with cord blood concentrations being approximately half those of maternal blood. The human data on placental concentrations are conflicting. Cadmium levels in human milk are approximately 5 to 10 percent of those found in blood (ATSDR, 1993a).

Cadmium absorption appears to involve sequestering by metallothionein, and plasma cadmium is found primarily bound to this protein. This binding appears to protect the kidney from the otherwise toxic effects of cadmium. It has been suggested that kidney damage by cadmium occurs primarily due to unbound cadmium (ATSDR, 1993a). Once cadmium is absorbed, it is eliminated slowly; the biological half-life has been estimated at 10 to 30 years (U.S. FDA, 1993).

Body stores of iron, zinc, and calcium may affect absorption and retention, although the retention may not be in readily available tissues (e.g., intestinal wall versus blood). The greatest concentrations of cadmium are typically found in the liver and kidney. Cadmium is not directly metabolized, although the cadmium ion binds to anionic groups in proteins, especially albumin and metallothionein (ATSDR, 1993a).

5.2.2.3 Acute Toxicity—

Effects of acute oral exposure to cadmium include GI irritation, nausea, vomiting, abdominal pain, cramps, salivation, and diarrhea. In humans, lethal doses caused massive fluid loss, edema, and widespread organ destruction. The ingested doses were 25 mg/kg and 1,500 mg/kg (ATSDR, 1993a).

5.2.2.4 Chronic Toxicity—

Kidney toxicity is a significant concern with cadmium exposure. Increased death rates from renal disease have been observed in exposed human populations in Belgium, England, and Japan (ATSDR, 1993a). There are also extensive animal data indicating that the kidney is a target organ. IRIS contains an RfD of 0.001 mg/kg/d in food based upon a NOAEL of 0.005 mg/kg/d in multiple human studies of waterborne cadmium. The critical effect was significant proteinuria (an indicator of kidney toxicity). To calculate the RfD, it was assumed that 2.5 percent of cadmium in food was absorbed and approximately 5 percent in water was absorbed. Using an uncertainty factor of 10 to account for intrahuman variability in cadmium sensitivity, the RfD for cadmium in food was calculated to be 0.001 mg/kg/d. The RfD was calculated using a toxicokinetic model to determine the highest level of cadmium in the human renal cortex not associated with significant proteinuria (IRIS, 1993).

The FDA has calculated a tolerable daily intake of 55 µg/person/day, which is approximately equal to 0.78 µg/kg/d (7.8×10^{-4} mg/kg/d) in a 70-kg person and 5.5 µg/kg/d (0.005 mg/kg/d) in a 10-kg child (their example uses 2+ years of age). The FDA value is based upon a pharmacokinetic approach that utilized the critical body burden associated with kidney toxicity. See FDA (1993) for more details.

ATSDR has also recently calculated a risk value for oral exposure based on kidney toxicity in humans. They developed a chronic MRL of 7×10^{-4} mg/kg/d based on a NOAEL of 0.0021 mg/kg/d in a large human cohort. The critical endpoint was an elevation of urinary beta-(2)-microglobulin. A toxicity threshold was estimated using a kinetic model of cadmium metabolism that predicted that approximately 5 percent of nonsmokers will reach or exceed the dose required to cause an effect at the NOAEL. To calculate the MRL, ATSDR used an addition uncertainty factor of 3 to account for sensitive members of the population. However, the critical study used a large population that included the elderly, who are considered a sensitive subpopulation (ATSDR, 1993a). The MRL developed by ATSDR is within 1 order of magnitude of the RfD developed by IRIS.

Cadmium causes many other types of toxic effects in addition to nephrotoxicity. In humans, some studies have suggested an association between neurotoxicity and cadmium exposure at levels below those that cause kidney toxicity (no additional details available). Cadmium exposure reduces the GI uptake of iron, which may cause anemia if iron intakes are low. Bone disorders including osteomalacia, osteoporosis, and spontaneous bone fracture have been observed in some chronically exposed individuals. Increased calcium excretion associated with cadmium-induced renal damage may lead to increased risk of osteoporosis, especially in postmenopausal women, many of whom are already at risk of osteoporosis. Cardiovascular toxicity and elevated blood pressure has been suggested in some human studies; however, the results are conflicting (ATSDR, 1993a).

Animal studies indicate that cadmium causes a wide variety of alterations in the function of the immune system. Some aspects of the system were enhanced and others were impaired (e.g., susceptibility to virally induced leukemia). In short-term studies, serious effects occurred at levels as low as 1.9 mg/kg/d and less serious effects (induction of antinuclear antibodies) at 0.57 mg/kg/d in a 10-week study in mice (ATSDR, 1993a). No longer-term studies were located for this work. An alternative exposure could be calculated for immunological effects based on the above study. The standard uncertainty factors used in this calculation would typically take into consideration inter- and intraspecies variability, use of a less than lifetime study, and the use of a LOAEL rather than a NOAEL. Immunological effects require further investigation to determine whether this is an effect that occurs in humans. It appears to be a sensitive endpoint for chronic exposure toxicity.

5.2.2.5 Developmental Toxicity—

Developmental toxicity has been associated with cadmium exposure both in short- and long-term studies. In 10-day prenatal dosing studies in rats at 18.4 mg/kg, malformations including split palate and dysplasia of the facial bones were observed with a NOAEL of 6.1 mg/kg/d. A similar study in rats found delayed ossification at 2 mg/kg/d. Other studies have found gross abnormalities and reduced weight in the range of 2 to 20 mg/kg/d (ATSDR, 1993a). Oral cadmium exposure of young mice depresses their humoral immune responses; the study did not find the same effect in adult mice (ATSDR, 1993a).

More sensitive measures of effects for cadmium have identified effects at much lower doses. ATSDR has determined that:

> the most sensitive indicator of development toxicity of cadmium in animals appears to be neurobehavioral development, which was impaired in offspring of female rats orally exposed to cadmium at a dose of 0.04 mg/kg/day prior to and during gestation . . . (ATSDR, 1993a).

Reduced locomotor activity and impaired balance were noted at a LOEL of 0.04 mg/kg/d with 11 weeks of exposure occurring prior to and during gestation. The effects were also observed at 0.7 mg/kg/d with exposure occurring only during gestation. Neurobehavioral effects were observed in other developmental studies and in chronic studies of effects in adult animals. Two studies yielding similar results were conducted with maternal exposures of 4.3 to 17.2 µg/mL of water (see numerous citations in Baranski et al., 1983).

Studies of developmental toxicity in human populations have been conducted on women exposed via inhalation in the workplace. Decreased birth weight has been reported in two studies, one with statistically significant results and the other lacking statistical significance. Inhalation studies in animals have found structural and neurobehavioral abnormalities similar to those found in the oral dosing studies (ATSDR, 1993a).

Based on the mutagenicity data results (discussed below), heritable defects may result from exposure to cadmium. However, mutagenicity assays do not provide dose-response data suitable for use for the calculation of a risk value. Calcium deficiency has been shown to increase the fetotoxicity of cadmium, and lindane exposure increased developmental toxicity in animal studies (ATSDR, 1993a).

Based on the reviewed information, neurobehavioral effects appear to be a critical endpoint for developmental effects as indicated by the LOEL of 0.04 mg/kg/d. The standard uncertainty factors used in the calculation of an exposure limit would typically take into consideration inter- and intraspecies variability and the use of a LOEL rather than a NOAEL.

Estimating an exposure limit for cadmium based on developmental toxicity is problematic because the average daily dose is approximately 0.03 mg/d (ATSDR, 1993a), which is equivalent to 4×10^{-4} per mg/kg/d in a 70-kg individual. The exposure for developmental effects, which would be calculated using the neurobehavioral LOEL noted above (approximately 4×10^{-5} mg/kg/d), is one-tenth of the average background consumption rate. Due to the margin of safety introduced by these factors, the estimated exposure limit should be viewed in the context of the overall exposure of population groups from all sources, as well as the benefits of fish consumption. Balancing risks and benefits is discussed in Volume 3 in this series, *Risk Management.*

5.2.2.6 Mutagenicity—

Results of bacteria, yeast, and human lymphocyte assays have been mixed. Positive results were observed in chromosomal aberration studies on human lymphocytes treated both in vitro and obtained from exposed workers. Mouse and hamster germ cell studies indicate that cadmium may interfere with spindle formation resulting in aneuploidy. Positive results have also been obtained in Chinese hamster ovary and mouse lymphoma cell assays (IRIS, 1993).

5.2.2.7 Carcinogenicity—

No animal or human oral exposure studies suggest that cadmium is carcinogenic via the oral exposure route. Animal studies conducted at relatively low exposure levels (up to 4.4 mg/kg/d) have yielded negative results. Studies have been conducted on population groups in high cadmium exposure areas and organ-specific cancer rates have been examined (kidney, prostate, and urinary tract). Most studies yielded negative results. A study in Canada found that elevated rates of prostate cancer paralleled the elevated cadmium exposure of the populations studied. ATSDR concluded that there was little evidence of an association between cadmium exposure and increased cancer risk in humans but that the statistical power of the studies to detect an effect was not high. They determined that neither the human nor animal studies provided sufficient evidence to determine the carcinogenic status of cadmium (ATSDR, 1993a).

Cadmium is classified as a probable human carcinogen (B1) by EPA based on **inhalation** studies in humans. The airborne cancer potency is 1.8×10^{-3} per µg/m^3 (IRIS, 1993).

5.2.2.8 Special Susceptibilities—

Populations with genetically determined lower ability to induce metallothionein are less able to sequester cadmium. Populations with depleted stores of dietary components such as calcium and iron due to multiple pregnancies and/or dietary deficiencies may have increased cadmium absorption from the GI tract. As stated above, increased calcium excretion associated with cadmium-induced renal damage may lead to increased risk of osteoporosis, especially in postmenopausal women. The relationship between cadmium toxicity and iron levels is not well established; however, in some studies it appears that iron-deficient individuals may be at greater risk. Individuals with kidney disease, diabetes, and age-related decreased kidney function may be at greater risk of cadmium-induced kidney toxicity (ATSDR, 1993a).

Immunological effects may be of concern for children because it appears, based upon animal studies, that young individuals may be at greater risk than adults. In addition, the immune system is not fully developed in humans until approximately 12 years of age. Immunological effects have also been observed in multiple animal studies of adults. These pose special risks for individuals with compromised immune systems (e.g., those with AIDS).

A variety of types of developmental effects have been associated with cadmium exposure (see discussion above). These all pose special risks for infants and children, as well as women of reproductive age.

5.2.2.9 Interactive Effects—

Dietary deficiencies of calcium, protein, zinc, copper, iron, and vitamin D may cause increased susceptibility to adverse skeletal effects. Animal studies have found an association between lindane and increased developmental toxicity and between calcium deficiency and increased fetotoxicity. Ethanol increased liver toxicity and garlic decreased kidney toxicity. Lead increased neurotoxicity and selenium decreased the clastogenic effect of cadmium on bone marrow. Exposure to chemicals that induce metallothionein (e.g., metals) reduced toxicity with parenteral cadmium exposure (ATSDR, 1993a).

MIXTOX reports a number of interactive studies on cadmium and selenium compounds. The studies have yielded mixed results with reports of inhibition, potentiation, additive effects, and no effects (MIXTOX, 1992).

5.2.2.10 Critical Data Gaps—

A joint team of scientists from ATSDR, National Toxicology Program (NTP), and EPA have identified the following data gaps: immunotoxicity, neurotoxicity, and

developmental toxicity in human populations, quantitative data on acute and intermediate toxicity in humans, and chronic exposure studies in humans using sensitive indicators of kidney toxicity, animal and human studies of carcinogenic effects, human genotoxicity, animal reproductive, immunotoxicity, and pharmacokinetic studies (ATSDR, 1993a).

5.2.2.11 Summary of EPA Levels of Concern—

Chronic Toxicity	1×10^{-3} mg/kg/d
Carcinogenicity	Probable inhalation carcinogen (B1). Insufficient data to determine carcinogenic status via oral exposure route.

5.2.2.12 Major Sources—

ATSDR (1993a), HSDB (1993), IRIS (1993), U.S. FDA (1993).

5.2.3 Mercury

5.2.3.1 Background—

Mercury is widely distributed in the environment due to both natural and anthropogenic processes. It is released generally as elemental mercury (Hg^0) or divalent mercury (Hg^{2+}). It can be converted between these forms and may form mercury compounds by chemical processes in air, water, and soil. Biological processes in other media, primarily soil and sediment, can convert inorganic mercury into organic, mostly methylmercury.

In fish tissue, the majority of mercury is methylmercury. Generally, the amount of mercury in fish tissue increases with the age and the size of the fish. The accumulation of mercury in fish varies among species; for the most part, the fish-eating species of fish accumulate higher concentrations of mercury than do non-piscivorous fish. Mercury is found in highest concentrations in organs and muscle.

Data on mercury toxicity have been reviewed for inclusion in IRIS. Currently there are both RfDs and cancer assessments in IRIS for elemental mercury, inorganic mercury (mercuric chloride), and methylmercury. EPA, in response to a mandate of the Clean Air Act Amendments of 1990, has prepared a multivolume *Mercury Study Report to Congress*. This has been extensively peer reviewed including a recent review by the Science Advisory Board (SAB). At this time, the *Mercury Study Report to Congress* has not been released as final. The SAB review draft is available from NTIS.

Methylmercury has also been the subject of evaluation by numerous States. Detailed analyses have been conducted in some specific areas, including evaluation of data regarding blood and hair mercury levels, toxic effects, and biological half-life values to estimate safe consumption levels of contaminated fish (Shubat, 1991, 1993a; Stern, 1993).

As discussed in previous sections, a total exposure assessment is beyond the scope of this document. Readers may wish to consult other sources to obtain information on background levels of methylmercury in the environment. Additional information on dietary sources of mercury is available in the FDA *Adult Total Diet Study*, conducted from October 1977 through September 1978, which contains information on total mercury content (not restricted to methylmercury) in a number of foods (Podrebarac, 1984). Readers are also referred to Volume III, *An Assessment of Exposure from Anthropogenic Mercury Emissions in the United States* of the *Mercury Study Report to Congress* (U.S. EPA, 1996a).

5.2.3.2 Pharmacokinetics—

Methylmercury is rapidly and nearly completely absorbed; EPA and ATSDR have used an estimate of 95 percent absorption following oral exposure (ATSDR, 1994; U.S. EPA, 1996e), and the World Health Organization (WHO) has similarly estimated an absorption of 90 to 100 percent for methylmercury (WHO, 1990).

Methylmercury is lipophilic, allowing it to pass through lipid membranes of cells and facilitating its distribution to all tissues, following absorption from the gastrointestinal tract. Methylmercury also binds readily to proteins. Methylmercury is found throughout fish tissue, and a substantial portion of the mercury in fish can be found in trimmed filets. Because of this, methylmercury exposure is not significantly reduced by trimming fat and skin from fish prior to cooking.

The highest methylmercury levels in humans are generally found in the kidneys. Methylmercury in the body is considered to be relatively stable and is only slowly demethylated to form mercuric mercury. In experiments on animals, females eliminated mercury more slowly than males, and young animals more slowly than adults. Neonatal excretion is slowed by the immaturity of the transport system. Methylmercury readily crosses the placental and blood/ brain barriers. Estimates for the half-life of methylmercury range from 44 to 80 days (U.S. EPA, 1996). Excretion of methylmercury is via the feces, urine, and breast milk. Methylmercury is distributed to human hair and to the fur and feathers of wildlife; measurement of mercury in these materials has served as a useful biomonitor of contamination levels.

5.2.3.3 Acute Toxicity—

Acute high-level exposures to methylmercury may result in kidney damage and failure, gastrointestinal damage, cardiovascular collapse, shock, and death. The estimated lethal dose is 10 to 60 mg/kg (ATSDR, 1994). An acute/ intermediate oral MRL of 1.2×10^{-4} was calculated by ATSDR using the Iraqi data on in utero exposed children described in Section 5.2.3.4.

5.2.3.4 Chronic Toxicity—

Although both elemental and methylmercury produce a variety of health effects at relatively high exposures, neurotoxicity is the effect of greatest concern; this is so

whether exposure occurs to the developing embryo or fetus during pregnancy or to adults and children.

Exposure of humans to methylmercury has generally been through consumption of contaminated food. Two major episodes of methylmercury poisoning through fish consumption have occurred. The first occurred in the early 1950s among people and wildlife living near Minamata City on the shores of Minamata Bay, Kyushu, Japan. The source of the methylmercury contamination was effluent from a chemical factory that used mercury as a catalyst; it accumulated in the tissue of fish and shellfish that were a routine part of the diet in these populations. Average fish consumption was reported to be in excess of 300 g/d (reviewed by Harada et al., 1995); this is a level of fish consumption that is almost 50 times greater than is typical (6.5 g/d) for the general U.S. population.

Symptoms of Minamata disease in children and adults included the following: impairment of the peripheral vision, disturbances in sensations ("pins and needles" feelings, numbness) usually in the hands and feet and sometimes around the mouth, incoordination of movements as in writing, impairment of speech, impairment of hearing, impairment of walking, and mental disturbances. It sometimes took several years before people were aware that they were developing the signs and symptoms of methylmercury poisoning. Over the years, it became recognized that nervous system damage could occur to the fetus if the mother ate fish contaminated with methylmercury during pregnancy.

In 1965, another methylmercury poisoning incident occurred in the area of Niigata, Japan. As in Minamata, multiple chemical plant sources of the chemical were considered. The signs and symptoms of disease in Niigata were those of methylmercury poisoning and the disease in Minamata.

Methylmercury poisoning occurred in Iraq following consumption of seed grain that had been treated with a fungicide containing methylmercury. The first outbreak occurred prior to 1960; the second outbreak of methylmercury poisoning from grain consumption occurred in the early 1970s. Imported mercury-treated seed grains arrived after the planting season; the grain was ground into flour and baked into bread. Unlike the long-term exposures in Japan, the epidemic of methylmercury poisoning in Iraq was short in duration. Because many of the people exposed to methylmercury in this way lived in small villages in very rural areas (and some were nomads), the total number of people exposed to these mercury-contaminated seed grains is not known. The number of people admitted to the hospital with symptoms of poisoning has been estimated to be approximately 6,500, with 459 fatalities reported.

As in the Japanese poisoning incidents, the signs and symptoms of disease were predominantly in the nervous system: difficulty with peripheral vision or blindness, sensory disturbances, incoordination, impairment of walking, slurred speech, and, in some cases, death. Children were affected as well as adults. Of great concern was the observation that infants, born of mothers who had consumed the methylmercury-contaminated grain (particularly during the second trimester of

pregnancy), could show nervous system damage even though the mother was only slightly affected herself.

More recent studies have dealt with populations that are expected to be exposed to methylmercury as a consequence of routine consumption of fish and marine mammals. These have included studies of populations around the Great Lakes, in New Zealand (Kjellstrom et al., 1986a, b), in the Amazon basin (e.g., Lebel et al., 1996; Marsh et al., 1995), the Seychelles Islands (Marsh et al., 1995), and the Faroe Islands (Dahl et al., 1996). The last two studies are of large populations of children presumably exposed to methylmercury in utero. Very sensitive measures of developmental neurotoxicity in these populations are, at the time of this writing, still being analyzed and published.

Methylmercury health endpoints other than neurotoxicity were evaluated by EPA using established risk assessment guidelines. Data for endpoints other than developmental neurotoxicity were limited (see Section 5.2.3.5).

In 1985 EPA published an RfD for methylmercury in IRIS of 3×10^{-4} mg/kg/d. The critical effect was multiple central nervous system effects (including ataxia and paresthesia) in adults in the Iraqi population who had been exposed to methylmercury through consumption of contaminated grain (Clarkson et al., 1975). A LOAEL of 0.003 mg/kg/d (corresponding to a blood concentration of 200 µg/L) was determined from inspection of the data. An uncertainty factor of 10 was applied for the use of a LOAEL in the absence of a NOAEL. Since that time, EPA has received several critiques and submissions to IRIS that questioned whether this RfD, based on effects in adults, was protective against developmental effects. A reexamination of the RfD took place with consensus on a revised value, and the RfD became available on IRIS in May 1995. The basis, derivation, and uncertainty analysis of the current EPA RfD is described at length in Volume IV, *Health Effects of Mercury and Mercury Compounds*, *Mercury Study Report to Congress* (U.S. EPA, 1996a).

The current EPA RfD for methylmercury was based on data on neurologic changes in 81 Iraqi children who had been exposed in utero; that is, their mothers had eaten methylmercury-contaminated bread during pregnancy. The data were collected by interviewing the mothers of the children and by clinical examination by pediatric neurologists conducted approximately 30 months after the poisoning episode. The incidence of several endpoints (including late walking, late talking, seizures, or delayed mental development and scores on clinical tests of nervous system function) were mathematically modeled to determine a mercury level in hair (measured in all the mothers in the study) that was associated with no adverse effects. Delays in motor and language development were defined by the following criteria:

- Inability to walk two steps without support by 2 years of age
- Inability to respond to simple verbal communication by age 2 years among children with good hearing

- Scores on physical examination by a neurologist who assessed cranial nerve signs, speech, involuntary movements, limb tone, strength, deep tendon reflexes, plantar responses, coordination, dexterity, primitive reflexes, sensation, posture, and ability to sit, stand, walk, and run

- Assessment of mental development or the presence of seizures based on interviews with the child's mother.

In calculating the mercury level in hair that was associated with no adverse effects in children exposed in utero, EPA used a benchmark dose (in this instance the lower bound for 10 percent risk of neurological changes) based on modeling of all effects in children. This lower bound was 11 ppm methylmercury in maternal hair. A dose-conversion equation was used to estimate a daily intake of 1.1 µg methylmercury/kg body weight/day that, when ingested by a 60-kg individual, will maintain a concentration of approximately 44 µg/L of blood or a hair concentration of 11 µg mercury/g hair (11 ppm).

A composite uncertainty factor of 10 was used to account for the following: variability in the human population (particularly the variation in biological half-life and variability in the hair-to-blood ratio for mercury); lack of data on long-term sequelae of exposure; and the lack of a two-generation reproductive study. The resulting RfD for methylmercury is 1×10^{-4} mg/kg/d or 0.1 µg/kg/d.

The range of uncertainty in the methylmercury RfD and the factors contributing to this range were evaluated in qualitative and quantitative uncertainty analyses. The uncertainty analyses indicated that paresthesia (numbness or tingling) in the hands and feet and occasionally around the mouth in adults is not the most reliable endpoint for dose-response assessment because it is subject to the patient's recognition of the effect. Paresthesia in adults is no longer the basis for EPA's methylmercury RfD.

There are, however, uncertainties associated with the current RfD based on developmental effects from methylmercury in children exposed in utero. There are difficulties with reliability in recording and classifying events such as late walking in children because the data were collected approximately 30 months after the child's birth. In addition, the data were collected on a population that did not necessarily follow Western cultural practices or use Western calendars in the recording of events such as first steps or first words. It should be noted, however, that the endpoints used represented substantial developmental delays; for example, a child's inability to walk two steps without support at 2 years of age, inability to talk based on use of two or three meaningful words by 2 years, or presence of generalized convulsive seizures. There is both variability and uncertainty in the pharmacologic parameters that were used in estimating the ingested mercury dose. There is also a degree of uncertainty introduced by the size of the study population (81 mother-child pairs).

The RfD is supported by additional studies in children exposed in utero. These include investigations among Cree Indians in Canada and New Zealanders who

consume large amounts of fish. In these studies, the hair concentration of mercury was used to monitor mercury exposure over time. Conclusions by the investigators in their official reports cite developmental delays among the children born of mothers whose hair mercury concentrations during pregnancy were 6 to 18 ppm, consistent with the benchmark dose of 11 ppm. The published data on the pilot study portion of the ongoing work in the Seychelles (data on children of about 5 years of age) are also consistent with EPA's benchmark dose.

A recent review by the Science Advisory Board (SAB) determined that, at this time, the RfD based on the data on Iraqi children is scientifically sound as supported by data in published human and animal studies. The RfD is a risk assessment tool, not a risk management decision. Judgments as to a "safe" dose and exposure are decisions that involve risk management components.

All RfDs are defined as having a degree of uncertainty of perhaps an order of magnitude. The RfD may be considered to be the midpoint in an estimated range of an order of magnitude (a factor of 10 or two factors of 3). Assuming that the RfD of 1×10^{-4} mg/kg/d is the midpoint of an order of magnitude range of uncertainty, then the upper end of the RfD range is 3×10^{-4} mg/kg/d and the lower bound value is 7×10^{-5} mg/kg/d. It is useful to estimate the number of fish meals per week that would result in exposure at the RfD. For a 70-kg person, the RfD is 7×10^{-3} mg/d or 4.9×10^{-2} mg/wk. If one assumes an 8-oz (0.227-kg) meal size and a fish tissue contamination level of 0.2 ppm (0.2 mg/kg), then one fish meal per week would result in exposure at the RfD. Given that there is a range threefold above and below the point estimate of the RfD, this consumption limit spans as many as three fish meals per week or as few as one fish meal every 3 weeks. Calculation of fish tissue contamination ranges for one 8-oz fish meal per week using methylmercury as an example is provided in Section 3.2.2.1.

5.2.3.5 Developmental Toxicity—

There are data linking elemental, mercuric, and methylmercury with developmental effects; these were used by EPA to determine weight-of-evidence classifications as specified in the *Guidelines for Risk Assessment of Developmental Toxicants*. For methylmercury, there are data on developmental effects in rats, mice, guinea pigs, hamsters, and monkeys. As described above (and documented at length in Volume IV of the *Mercury Study Report to Congress* [U.S. EPA, 1996a]), there are convincing data from a number of human studies that methylmercury is a developmental toxicant resulting in subtle to severe neurologic effects depending on dose and individual susceptibility. According to EPA guidelines, methylmercury is classified as having sufficient human and animal data for developmental toxicity.

Methylmercury accumulates in body tissue; consequently, maternal exposure occurring prior to pregnancy can contribute to the overall maternal body burden and result in exposure to the developing fetus. As a result of this, it is advisable to reduce mercury exposure of girls and women with childbearing potential to reduce overall body burden. If a woman has been exposed to mercury, even if exposure

is reduced during pregnancy, the outcome of that pregnancy may be affected, depending on the timing and extent of prior exposure.

5.2.3.6 Mutagenicity—

Methylmercury appears to be clastogenic but not to be a point mutagen; that is, mercury causes chromosome damage but not small heritable changes in DNA. In humans, methylmercury is widely distributed in the body. There are data on animals indicating that methylmercury administered intraperitoneally reaches germ cells and may produce adverse effects in those cells. Sex-linked recessive mutations (a sign of chromosomal damage to germ cells) were increased in *Drosophila melanogaster* given methylmercury in the diet. Studies have reported increased incidence of chromosomal aberrations (Skerfving et al., 1970) or sister chromatid exchange (Wulf et al., 1986) in lymphocytes of humans ingesting mercury-contaminated fish or meat. Chromosome aberrations have been reported in cats treated in vivo and in cultured human lymphocytes in vitro. Evidence of DNA damage has been shown in a number of in vitro systems.

Using criteria in the *Guidelines for Mutagenicity Risk Assessment* (U.S. EPA, 1986c), the EPA has classified methylmercury as being of high concern for potential human germ cell mutagenicity. All that keeps methylmercury from the highest level of concern is the lack of positive results in a heritable mutation assay. The data on mutagenicity were not sufficient, however, to permit estimation of the amount of methylmercury that would cause a measurable mutagenic effect in a human population.

5.2.3.7 Carcinogenicity—

Experimental animal data suggest that methylmercury may be tumorigenic in animals. Dietary exposures of mice to methylmercury resulted in significant increases in the incidences of kidney tumors in males but not in females (U.S. EPA, 1996e). EPA has classified methylmercury as a Group C, possible human carcinogen, based on inadequate data in humans and limited evidence in animals. EPA has not calculated quantitative carcinogenic risk values for methylmercury (IRIS, 1997). It should be noted that all of the carcinogenic effects were observed in the presence of profound damage to the kidneys. Tumors may be formed as a consequence of repair in the damaged organs. The data from genotoxicity testing indicate that, although methylmercury is clastogenic (breaks chromosomes), it does not cause point mutations. Evidence points to a mode of action for methylmercury carcinogenicity that operates at high doses certain to produce other types of toxicity in humans. Given the levels of exposure most likely to occur in the U.S. population, even among consumers of large amounts of fish, methylmercury is not likely to present a carcinogenic risk to the U.S. population.

5.2.3.8 Special Susceptibilities—

The developing fetus is thought to be at increased risk from methylmercury exposure. There are not sufficient data on children exposed only after birth to

determine if this is a group with increased susceptibility to mercury toxicity. Children are considered to be at increased risk of methylmercury exposure by virtue of their greater food consumption (mg food/kg body weight) by comparison to adults. Additional risk may also result from the apparently decreased ability of young individuals to eliminate mercury (see Section 5.2.3.2). ATSDR has listed the following groups as particularly susceptible: people with impaired organ function (especially kidney, CNS, and liver) and individuals with a dietary insufficiency of zinc, glutathione, antioxidants, or selenium (ATSDR, 1994).

5.2.3.9 Interactive Effects—

Potassium dichromate and ethanol may increase the toxicity of mercury, although these effects have been noted only with metallic and inorganic mercury. Atrazine increases the toxicity of methylmercury in experimental animals. Vitamins D and E, thiol compounds, selenium, copper, and possibly zinc are antagonistic to the toxic effects of mercury (ATSDR, 1994). There is insufficient information to recommend quantitative changes in risk estimations based upon interactive effects.

5.2.3.10 Critical Data Gaps—

Additional data are needed on the exposure levels at which humans experience subtle, but persistent, adverse neurological effects. Data on immunologic effects and reproductive effects are not sufficient for evaluation of low-dose methylmercury toxicity for these endpoints.

5.2.3.11 Summary of EPA Levels of Concern—

Chronic Toxicity	1×10^{-4} mg/kg/d
Carcinogenicity	Insufficient data to determine carcinogenic status.
Developmental Toxicity	No developmental risk value calculated; the chronic toxicity RfD above was determined based on developmental effects.

5.2.3.12 Major Sources—

ATSDR (1994), IRIS (1995, 1997), Shubat (1993a), Stern (1993), U.S. EPA (1993a, 1995, 1996a).

5.2.4 Selenium

5.2.4.1 Background—

Selenium occurs naturally in many areas and is produced through industrial processes. It is an essential nutrient with a Recommended Dietary Allowance (RDA) of 55 µg/d (0.055 mg) for nonlactating women and 20 additional µg/d during lactation. ATSDR has identified daily intake at nontoxic levels of approximately 0.05 to 0.15 mg/d (ATSDR, 1989; HSDB, 1993). This is approximately equivalent

to 7×10^{-4} to 2×10^{-3} mg/kg/d in a 70-kg individual. The RDA for adult males is 70 µg/d (NRC, 1989). Selenium plays a critical role in the antioxidant enzyme glutathione peroxidase. Selenium deficiency has been associated with muscle degeneration in humans. A serious form of this, congestive cardiomyopathy (Keshan disease), has been studied in areas of China with low naturally occurring levels of selenium. It has also been shown to have a protective effect against chemically induced cancers in laboratory animals (Robbins et al., 1989). Although selenium is an essential nutrient, it is toxic at high exposure levels and is mutagenic in some test systems (ATSDR, 1989).

Definitive information concerning the chemical forms of selenium found in fish is not available (U.S. EPA, 1993a). Due to the lack of information on chemical forms, the toxicities of a variety of selenium forms are included in the discussion below. In some parts of the United States, particularly in western States, soil concentrations lead to selenium levels in plants that can cause human exposure at potentially toxic levels (ATSDR, 1989). This exposure should be considered in evaluating the overall exposure to selenium and in developing fish consumption advisories.

5.2.4.2 Pharmacokinetics—

Selenium contained in food is generally associated with proteins as organic selenium compounds. It is easily absorbed by the body and accumulates primarily in the liver and kidneys. It accumulates to a lesser extent in the blood, lungs, heart, testes, and hair (ATSDR, 1989). Detailed information on metabolism of selenium can be found in the *Toxicological Profile for Selenium.* This document also contains an extensive discussion of the selenium concentrations in human tissues and fluids correlated with specific health effects (ATSDR, 1989).

5.2.4.3 Acute Toxicity—

Signs of acute selenium poisoning include difficulty in walking, labored breathing, cyanosis of the mucous membranes, congestion of the liver, endocarditis and myocarditis, degeneration of the smooth musculature of the GI tract, gall bladder and bladder, and erosion of the long bones (IRIS, 1993). Subacute selenosis (prolonged exposure at relatively high doses) causes impaired vision, ataxia, disorientation, and respiratory distress (IRIS, 1993). Tachycardia has been reported in humans exposed to high doses; myocardial disorders have also been associated with selenium deficiencies. Acute exposure dog studies at high doses have found multiple alterations in blood chemistry (ATSDR, 1989).

5.2.4.4 Chronic Toxicity—

IRIS provides an RfD of 0.005 mg/kg/d for selenium and selenium compounds based on a NOAEL of 0.015 mg/kg/d from a 1989 human epidemiological study that found clinical selenosis at the LOAEL of 0.023 mg/kg/d. The NOAEL was calculated from regression analysis of blood selenium levels and selenium intake. An uncertainty factor of 3 rather than 10 was used for intraspecies variability (IRIS,

1993). Note that the NOAEL and LOAEL for selenium in the 1989 human study are only slightly higher than the average daily intake and the RDA (see above).

High levels of selenium exposure have caused the following effects: lowered hemoglobin levels, mottled teeth, skin lesions, CNS abnormalities, fatigue, anorexia, enlarged spleen, thickened and brittle nails, hair and nail loss, decreased blood clotting ability, liver dysfunction, and muscle twitching (IRIS, 1993). Humans exposed to high dietary levels have reported GI disturbances (dose unspecified). Cows with high naturally occurring dietary exposures were found to have ulcers in the upper GI tract (ATSDR, 1989).

Lifetime exposure of mice to sodium selenate or sodium selenite at 0.31 mg/kg/d caused amyloidosis of the lung, liver, kidney, and heart. Mice appear to be more sensitive to selenium with regard to lung toxicity than rats. Rats may be more sensitive to the cardiotoxic effects, with an LEL of 0.1 mg/kg/d in a chronic study (the study had some deficits in study design) (ATSDR, 1989).

Hematological effects have been observed in multiple acute and chronic animal studies. No human studies were located for this report or by ATSDR in their literature review. Rats subchronically exposed to wheat containing selenium at a dose of 0.68 mg/kg/d for 6 weeks had a reduction of blood hemoglobin. At 0.75 mg/kg/d in a similar study, red cell hemolysis was observed (ATSDR, 1989).

Bone softening in livestock has been noted with an LEL of 0.2 mg/kg/d with exposure over several months (less than 100 days). Adverse effects on the liver have been observed in multiple animal studies with LELs of 0.8 mg/kg/d and above. Kidney damage has also been noted with an LEL of 0.31 mg/kg/d. Dermal effects have been observed at doses as low as 0.053 mg/kg/d in humans with dietary exposure (ATSDR, 1989). This observation served as a partial basis for the calculation of an MRL by ATSDR. Depression of the immune system was observed in rats exposed subchronically to sodium selenite at 0.75 mg/kg/d. At lower doses (0.075 mg/kg/d and 0.28 mg/kg/d), mixed results were obtained, with a stimulation of some components of the immune system and depression of others. No NOEL was identified in the study (ATSDR, 1989).

Chronic exposure studies in animals have identified multiple adverse effects on the reproductive ability of animals and on offspring viability. Effects include: reduced rates of conception at 0.41 mg in pigs exposed from 8 weeks of age (other offspring effects are listed under developmental effects), abnormal length estrus cycles in rats exposed subchronically to 0.34 mg/kg/d, increased fetal resorption and decreased conception rate in livestock exposed at an LEL of approximately 0.5 mg/kg/d, failure to breed in a three-generation study of mice exposed at 0.42 mg/kg/d, no effects in a two-generation study of mice at 0.21 mg/kg/d, and a 50 percent reduction in the number of young successfully reared with maternal exposure to 0.35 mg/kg/d for 1 year. Male fertility did not appear to be affected in the results reported, although the testes are a storage site for selenium (ATSDR, 1989).

Neurological symptoms have been reported in human and animal studies. A family exposed to approximately 0.26 mg/kg/d via drinking water reported various symptoms of selenosis including listlessness and a lack of mental alertness. Effects ceased when the water use was discontinued. More severe effects have been observed in high-selenium areas of China. Peripheral anesthesia and pain in the limbs were reported, although no associated estimate of exposure was provided. Exaggerated tendon reflexes, convulsions, paralysis, and hemiplegia were estimated to occur at a minimum chronic exposure of 0.053 and an average of 0.083 mg/kg/d. A NOAEL of 0.025 was estimated. This information was used by ATSDR to calculate a chronic exposure MRL of 0.003 mg/kg/d (ATSDR, 1989).

Neurological effects identified in animal studies include: drowsiness, lethargy, ataxia, paralysis, bilateral lesions in the spinal cord, impaired vision, aimless wandering behavior, and neuronal degeneration of the cerebral and cerebellar cortices. Many of these were observed at relatively high doses; however, the neuronal degeneration was observed at an LEL of 0.6 mg/kg/d dosing with sodium selenite mixed in food (ATSDR, 1989).

The IRIS RfD and ATSDR MRL are within 1 order of magnitude of each other. The IRIS value was used to calculate fish consumption limits shown in Section 4 for chronic exposure toxicity. Please see the note at the end of the Developmental Toxicity section for cautions regarding this use of these values.

5.2.4.5 Developmental Toxicity—

Limited information is available on the developmental toxicity of selenium in humans. One anecdotal report indicated that selenium exposure may be associated with spontaneous abortion and skeletal abnormalities (ATSDR, 1989); however, the anecdotal nature of the report makes it inappropriate for drawing conclusions regarding causality.

In animals, selenium has caused growth retardation, decreased fertility, embryotoxicity, fetotoxicity, and teratogenic effects. One researcher noted that, in a high-selenium area, teratogenic effects were not seen in humans, but they were observed in chickens (IRIS, 1993).

A multigeneration study in mice dosed with selenate at 0.39 mg/kg/d identified a significant increase in young deaths in the F1 generation and increased runts in the F1 through F3 generations. Because only one dose was used, only a LOEL can be obtained from this study. A one-generation mouse study found a NOEL of 0.39 mg/kg/d. An early five-generation study identified a NOEL of 0.075 mg/kg/d and a LOEL of 0.125 mg/kg/d with a 50 percent reduction in the number of young reared at that dose. There are multiple possible reasons for the reduction, including decreased fertility; consequently, it is not appropriate for use in calculating an exposure limit for developmental effects. A recent study in primates identified no developmental effects up to 0.3 mg/kg/d. However, the study utilized dosing over a portion of the pregnancy, and, unlike the multigenerational studies,

it did not include dosing prior to and during all of the pregnancy or dosing of the neonates (IRIS, 1993).

Multiple studies have determined that exposure of livestock (e.g., sheep, pigs, cattle) to naturally seleniferous diets resulted in fetal malformations and interference with normal fetal development. Malformations were associated with other manifestations of toxicity. The specific selenium compounds associated with these effects have not been identified (ATSDR, 1989). At 0.41 mg, pigs exposed from 8 weeks of age had offspring with significantly reduced birth weight and weaning weights (ATSDR, 1989).

ATSDR has reported studies on experimental animals that have yielded the following results: prenatal exposure at 0.34 mg/kg/d caused reduced fetal growth with a NOAEL of 0.17 mg/kg/d; mice exposed to 0.42 mg/kg/d for three generations had an increased incidence in fetal deaths and a high proportion of runts among survivors; macaques exposed prenatally at levels up to 0.3 mg/kg/d exhibited no adverse effects. It was noted that exposure to inorganic selenium compounds at levels that are not maternally toxic have not produced teratogenic effects (ATSDR, 1989). (EPA's guidelines on developmental toxicity specify that dosing should include doses that cause some level of maternal toxicity; therefore, this is not cause for dismissing the study results.)

Based on the reviewed information, the multigeneration mouse study cited in IRIS with a LOEL of 0.39 mg/kg/d appears to be the most appropriate value for calculating an estimated exposure limit for developmental effects because there are no other appropriate studies that provide data on long-term maternal and offspring exposure effects. There is concern regarding the use of these results because severe effects were seen at the LOEL and because severe effects have been observed in other studies at approximately the same exposure level. The standard uncertainty factors used to calculate an estimated exposure limit would typically take into consideration inter- and intraspecies variability and the use of a LOEL rather than a NOEL. A modifying factor for the severity of effects at the LOEL could also be applied. The resulting value is within 1 order of magnitude of an exposure limit that could be calculated from the NOEL of 0.17 mg/kg/d for reduced fetal growth (as reported by ATSDR). Due to the longer-term nature of the dosing, the multigeneration study cited in IRIS may be more appropriate.

Note: Decisions regarding thresholds for adverse effects of selenium are complex because selenium is an essential nutrient. Consequently, the application of uncertainty factors in the standard manner may not be appropriate. Some exposure to selenium is necessary, as indicated by the RDA. There appears to be a relatively small margin between the effective/necessary dose and the toxic dose for this chemical. Additionally, the need for selenium and the toxicity of selenium is expected to vary among individuals. Consequently, it is necessary to evaluate the overall exposure to selenium in order to evaluate potential risks and make well-informed decisions regarding exposure limits. Decisions regarding the contribution to total selenium exposure that can come from fish without generating toxicity will depend on the cumulative exposures from other sources. This is expected to vary

considerably depending on the part of the country in which individuals reside, their dietary habits, and other factors. If these factors were not a consideration for selenium exposure, an additional modifying factor would be recommended when estimating exposure limits for developmental effects due to the serious nature of effects observed in multiple species at or near the LEL of 0.39. Readers should carefully review the toxicity data regarding selenium and determine the appropriate exposure limit for developmental effects, based on the exposures anticipated in their States and their interpretation of the toxicological and epidemiological literature. See also Abernathy et al. (1993) for additional guidance on this topic.

It will be necessary to obtain a NOEL from a multigeneration study and to further explore the mechanisms of fetal and neonatal lethality associated with selenium exposure to adequately determine the appropriate exposure limit for developmental effects. A well-designed human epidemiological study of prenatally exposed individuals from high naturally occurring selenium areas is needed to provide insight into human effects of selenium exposure.

5.2.4.6 Mutagenicity—

There are many positive mutagenicity assays on selenium compounds including unscheduled DNA synthesis, increased chromosomal aberrations in human lymphocytes and in the bone marrow of rats, and an increase in sister chromatid exchanges in human whole-blood cultures. There are also assays with negative results (IRIS, 1993).

Inorganic selenium compounds appear to have genotoxic effects at relatively high doses and antigenotoxic effects at lower doses. For example, a study of mice exposed to mutagens and given doses of 0.05 to 0.125 mg/kg/d of selenium indicates that selenium may inhibit the mutagenic effects of chemical agents (ATSDR, 1989). For a summary of study results, see the *Toxicological Profile for Selenium* (ATSDR, 1989).

5.2.4.7 Carcinogenicity—

EPA has determined that there are insufficient data to assess the carcinogenic potency of selenium. EPA has classified selenium sulfide as a probable human carcinogen (B2), based on liver and lung tumors in oral exposure studies in multiple species (IRIS, 1993). Some human studies indicated that combined vitamin E and selenium **deficiencies** may lead to higher cancer risks (ATSDR, 1989).

5.2.4.8 Special Susceptibilities—

ATSDR has listed the following groups as potentially having greater susceptibility: pregnant women and their fetuses, persons exposed to high fluoride levels in drinking water (evidence equivocal), those with vitamin E deficiencies, and populations with elevated exposures arising from exposure via food produced in high-selenium areas (ATSDR, 1989).

Based on the occurrence of adverse effects reported in human and animal studies, individuals with diseases or disorders of the following organ systems may be at greater risk from selenium exposure than the general population: hematopoietic, dermal, nervous, liver, kidney, cardiac, and immune systems.

HSDB listed individuals with the following conditions as requiring additional protection: chronic indigestion or a history of peptic ulceration; skin, lung, kidney or liver disease; dermatitis; chronic bronchitis; skin allergy or respiratory tract infection; jaundice; or albuminuria (HSDB,1993). Their cautions are based on all routes of selenium exposure.

5.2.4.9 Interactive Effects—

Selenium alters the toxicity of many chemicals. It reduces the toxicity of mercury, cadmium, lead, silver, and copper; some forms reduce arsenic toxicity. Detailed information on specific interactions can be found in the *Toxicological Profile for Selenium* (ATSDR, 1989). Selenium also interacts with vitamins, sulfur-containing amino acids, xenobiotics, and essential and nonessential elements. ATSDR notes that most interactions are beneficial (ATSDR, 1989).

5.2.4.10 Critical Data Gaps—

ATSDR has reported the following data gaps: human epidemiological data for all relevant effects, relationship between selenium dietary exposure levels and cancer, mechanisms of genotoxicity, reproductive, developmental studies regarding cataract formation, immunotoxicity, neurotoxicity, especially behavioral and histopathological CNS effects, pharmacokinetic, and bioaccumulation, and bioavailability from environmental media (ATSDR, 1989). A multigeneration study that utilizes sensitive endpoints for toxicity is needed to develop a more adequately based exposure limit for developmental effects.

5.2.4.11 Summary of EPA Levels of Concern—

Chronic Toxicity	5×10^{-3} mg/kg/d
Carcinogenicity	Insufficient data to assess carcinogenicity. Note that selenium sulfide is classified as a Group B2 carcinogen.

5.2.4.12 Major Sources—

ATSDR (1989), HSDB (1993), IRIS (1993).

5.2.5 Tributyltin Oxide

5.2.5.1 Background—

Tributyltin oxide belongs to the organometallic family of tin compounds that have been used as biocides, disinfectants, and antifoulants. This compound (and other tributyltin compounds) have high bioconcentration factors in aquatic organisms

and are acutely and chronically toxic to these organisms at low concentrations. Because of concerns over these compounds' effects on nontarget aquatic species, in 1986 EPA initiated a special review of tributyltin compounds used as antifoulants (U.S. EPA, 1986f). In 1988, the Organotin Antifouling Paint Control Act (OAPCA) was enacted, which contained interim and permanent tributyltin restrictions as well as environmental monitoring, research, and reporting requirements.

The tributyltin compounds registered for use as antifoulants are: tributyltin oxide, tributyltin adipate, tributyltin dodecenyl succinate, tributyltin sulfide, tributyltin acetate, tributyltin acrylate, tributyltin fluoride, tributyltin methacrylate, and tributyltin resinate (U.S. EPA, 1986f). This toxicological profile discusses only tributyltin oxide, since this is the only tributyltin compound with risk assessment information (an RfD) and there is more toxicological information on this compound than any other.

5.2.5.2 Pharmacokinetics—

The pharmacokinetic information available consists of data on organotin compounds as a group; there are few data specific to tributyltin oxide. Organotin compounds appear to be absorbed in mammals, with studies in rats showing detection of tin compounds in the gastrointestinal tract, kidney, and liver, with little retention observed in the brain and blood. One study specific to tributyltin oxide found the highest levels of tin in the liver and kidneys, with levels in the brain and adipose tissue at 10 to 20 percent of the liver and kidney levels. The metabolism of organotin compounds appears to involve dealkylation, with the liver as the active site. There are no data regarding the excretion of organotin compounds (ATSDR, 1992e).

5.2.5.3 Acute Toxicity—

The limited available data show tributyltin to be quite toxic to animals, with LD_{50}s ranging between 122 and 194 mg/kg in rats (ATSDR, 1992; HSDB, 1997). No other information is available on the acute effects of tributyltin oxide.

5.2.5.4 Chronic Toxicity—

There are no studies on the effects of tributyltin oxide in humans. Animal studies have shown effects on the blood (lowered corpuscular volume and hemoglobin mass and decreased leukocytes) and liver, and immunological effects including thymus atrophy and depletion of T-lymphocytes in the spleen and lymph nodes from tributyltin exposure (ATSDR, 1992; HSDB, 1997).

IRIS provides an RfD for tributyltin oxide of 3.0×10^{-5} mg/kg/d, based on a NOAEL of 0.025 mg/kg/d and an uncertainty factor of 1,000. This was based on a chronic rat feeding study in which immunotoxicity was observed. The uncertainty factor of 1,000 reflects the uncertainty in extrapolating from laboratory animals to humans, the uncertainty in the range of human sensitivity, and the uncertainty due to the lack of important toxicological data (IRIS, 1997).

EPA has medium confidence in the studies on which the RfD was based, low confidence in the database, and low confidence in the RfD. This is based on the fact that the principal study was a well-designed and well-conducted chronic toxicity assay; however, the number of animals used in the study was somewhat minimal and only a preliminary report of the study was available for review. The low ranking in the database is due to a lack of independent confirmation of the critical effect, the lack of toxicological data for a second species, and the lack of information on reproductive toxicity (IRIS, 1997).

5.2.5.5 Developmental Toxicity—

No studies are available on the developmental effects of tributyltin oxide in humans. A study in mice reported dose-related decreases in fetal weights and some skeletal abnormalities, such as fused ribs and cleft palates, at all dose levels and also in the controls (ATSDR, 1992). When pregnant rats were exposed to high doses of tributyltin oxide, decreased numbers of live births and decreased growth and viability of the offspring were reported (HSDB, 1997).

5.2.5.6 Mutagenicity—

Results from in vitro studies on tributyltin oxide have been primarily negative. Tributyltin oxide was negative in a variety of studies with *Salmonella typhimurium* and Chinese hamster cells; the only positive results were with metabolic activation. In vivo studies were also mainly negative; the compound was negative in *Drosophila melanogaster* and in the micronucleus test (at cytotoxic doses) in mice. One positive result was obtained in the micronucleus test where increased micronuclei in erythrocytes were noted (ATSDR, 1992e; HSDB, 1997).

5.2.5.7 Carcinogenicity—

There are very limited data on the carcinogenicity of tributyltin oxide. No human studies are available and the one available animal study noted an increased incidence of some benign tumors at the highest dose level in rats. The authors concluded that their results could not be considered evidence of carcinogenicity, but that the changes may be related to a direct action of tributyltin oxide on the endocrine glands (ATSDR, 1992; HSDB, 1997). EPA has not classified tributyltin oxide for carcinogenicity.

5.2.5.8 Special Susceptibilities—

ATSDR reported that no studies were located regarding unusual susceptibility of any human subpopulation to tributyltin oxide. However, based on the target organ systems of organotin compounds, persons with liver disease, blood disorders, deficiencies of the immune system, neurobehavioral disorders, and perhaps kidney disease could be predisposed to adverse health effects of tributyltin oxide under appropriate conditions of exposure (ATSDR, 1992).

5.2.5.9 Interactive Effects—

Limited information is available on the interactive effects of tributyltin oxide. Sulfur-containing compounds have been shown, in vitro, to interact with tributyltin compounds to produce other compounds with lower hemolytic activity (ATSDR, 1992).

5.2.5.10 Critical Data Gaps—

The following are areas where data gaps exist for tributyltin oxide: acute, intermediate (14 to 365 days), and chronic exposures and reproductive, developmental, and neurotoxic studies.

5.2.5.11 Summary of EPA Levels of Concern—

Chronic Toxicity	3.0×10^{-5} mg/kg/d
Carcinogenicity	Insufficient data to determine carcinogenic status.

5.2.5.12 Major Sources—

ATSDR (1992), HSDB (1997), IRIS (1997), U.S. EPA (1986f).

5.3 ORGANOCHLORINE PESTICIDES

In addition to the discussions of individual target analytes, please refer to the discussion of toxicity characteristics of the organochlorine group in Appendix C.

5.3.1 Chlordane

5.3.1.1 Background—

Chlordane is an organochlorine pesticide comprised of the sum of cis- and trans-chlordane and trans-nonachlor and oxychlordane for purposes of health advisory development (U.S. EPA, 1993a). It was used extensively until most uses were banned in 1988. Due to its long half-life and ability to concentrate in biological materials, it is still widely distributed in fish in the United States.

5.3.1.2 Pharmacokinetics—

Chlordane bioaccumulates in biological materials (IRIS, 1993). It is highly lipophilic and readily absorbed via all routes. Chlordane is metabolized via oxidation, which results in a number of metabolites, including oxychlordane, that are very persistent in body fat. Reductive dehalogenation of chlordane forms free radicals, which are hypothesized to be significant in chlordane toxicity (ATSDR, 1992d).

Human studies have found chlordane in pesticide applicators, residents of homes treated for termites, and those with no known exposures other than background (e.g., food or airborne). Human milk fat contained a mean chlordane residue of approximately 188 ppm. Oxychlordane residues were detected in 68 percent of human milk samples in a low pesticide usage area and in 100 percent of the 50 samples tested in Hawaii. It is anticipated that all routes of exposure were involved in maternal exposure to chlordane. Fat accumulation of chlordane appears to depend on the exposure duration (ATSDR, 1992d).

Mechanisms of toxicity include: the binding of chlordane and its metabolites irreversibly to cellular macromolecules, causing cell death or disrupting normal cellular function; increasing tissue production of superoxide radicals, which accelerates lipid peroxidation and disrupts the function of membranes; possible suppression of hepatic mitochondrial energy metabolism; and alteration of neurotransmitter levels in various regions of the brain; a reduction in bone marrow stem cells prenatally; and suppression of gap junction intercellular communication (ATSDR, 1992d).

5.3.1.3 Acute Toxicity—

Chlordane is moderately to highly toxic with an estimated lethal dose to humans of 6 to 60 g (IRIS, 1993). See the listing of usual effects associated with organochlorine exposure in Appendix C.

5.3.1.4 Chronic Toxicity—

Chlordane has classic organochlorine toxicity as described in Appendix C. The principal systems affected by exposure are liver, nervous system, and immune system. Other effects include neurological abnormalities including grand mal seizures and altered EEG results (ATSDR, 1992d).

Reduced fertility and survivability in mice and rats has occurred at 25 and 16 mg/kg, respectively, and may be associated with reduced binding of progesterone in the endometrium or with altered metabolism and circulating levels of steroid hormones. The studies were not designed to identify thresholds or mechanisms for action (ATSDR, 1992d) and cannot be used to derive dose-response data for estimation of an RfD.

Jaundice has been reported in humans living in homes treated with chlordane for termite control. Chemistry changes indicative of altered liver function were observed in pesticide applicators in Japan who were exposed to chlordane (ATSDR, 1992d).

Multiple neurological effects have been reported in humans exposed both acutely and chronically. According to ATSDR, neither animal nor human studies have evaluated subtle neurological or behavioral effects that may occur at low levels. Consequently, it is not possible to assess the likelihood of human effects at environmental exposure levels (ATSDR, 1992d).

IRIS provides an RfD of 6.0×10^{-5} based on a NOAEL of 0.055 mg/kg/d in a study that found liver atrophy in female rats. The standard uncertainty factors of 10 each for inter- and intraspecies variability were applied. An additional safety factor of 10 was applied “to account for the lack of an adequate reproduction study and adequate chronic study in a second mammalian species, and the generally inadequate sensitive endpoints studied in the existing studies, particularly since chlordane is known to bioaccumulate over a chronic duration” (IRIS, 1993). Confidence in this RfD is low for these reasons (IRIS, 1993).

5.3.1.5 Developmental Toxicity—

According to the IRIS file, “there have been 11 case reports of CNS effects, blood dyscrasias and neuroblastomas in children with pre/postnatal exposure to chlordane and heptachlor” (IRIS, 1993). Data were insufficient to calculate an exposure limit for developmental effects from this study.

ATSDR reports a number of developmental effects. Prenatal and early postnatal exposure in mice may have permanent effects on the immune system, including a reduction in the number of stem cells required to form the mature immune system. Effects were observed at 4 mg/kg/d. Neurological effects include abnormal behavior and increased seizure thresholds in mice at 1 mg/kg/d prenatal and postnatal (via lactation) exposure (no NOEL was identified). Alterations in plasma

corticosterone levels were observed, which may result from a change in the neuroendocrinological feedback mechanisms (ATSDR, 1992d).

There is insufficient information to develop a well-based estimated exposure limit for developmental effects. According to ATSDR, neither animal nor human studies have evaluated subtle neurological or behavioral effects that may occur at low levels. Consequently, it is not possible to assess the likelihood of human effects at environmental exposure levels (ATSDR, 1992d). Neurological and behavioral effects may be the most sensitive measures of chlordane developmental toxicity. This appears to be the case for some other organochlorine pesticides (see DDT and toxaphene). However, it is not possible to estimate the threshold level because the LOEL caused multiple and serious effects. If readers elect to calculate an exposure limit for developmental effects, it should be considered a limited estimate due to the lack of information on the threshold for effects. The standard uncertainty factors used in this calculation would typically take into consideration inter- and intraspecies variability, the use of a LOEL rather than a NOAEL, and the poor quality of the database.

Chlordane accumulates in body tissues; consequently, exposure occurring prior to pregnancy can contribute to the overall maternal body burden and result in exposure to the developing individual. As a result, it is necessary to reduce exposure to children and females with childbearing potential to reduce overall body burden. If a female has been exposed to chlordane, even if exposure is reduced during pregnancy, the outcome of that pregnancy may be affected, depending on the timing and extent of prior exposure.

Regarding cancer in children, see the discussion in Section 5.3.1.7.

5.3.1.6 Mutagenicity—

Mutagenicity assays of chlordane have yielded mixed results, with positive results generally obtained in higher organism cell assays and negative results in bacterial assays (IRIS, 1993).

5.3.1.7 Carcinogenicity—

Chlordane is classified as a probable human carcinogen (B2) by EPA based on oral studies in animals. The oral cancer slope factor of 1.3 per mg/kg/d is the geometric mean of the cancer potencies calculated from four data sets (IRIS, 1992). This value was used to develop the fish consumption limits for carcinogenic toxicity listed in Section 4.

Positive results have been obtained in four strains of mice of both sexes and in male rats. In addition, numerous structurally related organochlorine pesticides have been found to be carcinogenic.

Neuroblastoma and acute leukemia have also been associated with prenatal and early childhood exposure to chlordane (ATSDR, 1993c).

5.3.1.8 Special Susceptibilities—

Based on the results of animal studies showing prenatal exposure causes damage to the developing nervous and immune systems, fetuses and children may be at greater risk than adults from chlordane exposure. According to ATSDR:

> Given the generally greater sensitivity to toxicants of incompletely developed tissues, it seems possible that prenatal exposure of humans to chlordane could result in compromised immunocompetence and subtle neurological effects. (ATSDR, 1992d).

Due to the interactive effects of chlordane with other chemicals via microsomal enzymes (see Section 5.3.1.9), ATSDR has cautioned that: “doses of therapeutic drugs and hormones may require adjustment in patients exposed to chlordane.” The results of an acute animal study suggest that protein-deficient diets may also increase the toxic effects of chlordane (ATSDR, 1992d).

ATSDR has listed the following populations as unusually susceptible: those with liver disease or impaired liver function; infants, especially those with a hereditary predisposition to seizures; and the fetus. In addition, it has been hypothesized that a subpopulation may exist with a predisposition to blood dyscrasias resulting from chlordane exposure. Identification of such a population is not now possible (ATSDR, 1992).

5.3.1.9 Interactive Effects—

Chlordane is a potent inducer of hepatic microsomal enzymes. (See a discussion of organochlorine effects related to this induction in Appendix C.) Chlordane exposure has been associated with an increased rate of metabolism of therapeutic drugs, hormones, and many other endogenous and xenobiotic compounds. Exposure to other chemicals that induce the same enzymes may increase the toxicity of chlordane by enhancing its metabolism to its toxic intermediate. The acute toxic effects of aldrin, endrin, and methoxychlor with chlordane were greater than the additive sum of the individual toxicities (ATSDR, 1992d).

It has been suggested that increased dietary vitamins C or E or selenium may be protective against free-radical-induced toxicity (ATSDR, 1992d).

MIXTOX reported synergistic effects between chlordane and endrin in mice exposed via gavage and both potentiation and inhibition with γ-hexachlorocyclohexane in rodents exposed via gavage. Synergism is reported with toxaphene and malathion together with chlordane in mice exposed via gavage (MIXTOX, 1992).

5.3.1.10 Critical Data Gaps—

IRIS lists the following data gaps for chlordane: chronic dog feeding study, rat reproduction study, rat teratology study, and rabbit teratology study (IRIS, 1993). It is clear from this list that the developmental effects of chlordane have not been adequately evaluated.

According to ATSDR, neither animal nor human studies have evaluated subtle neurological or behavioral effects that may occur at low levels. These types of studies are needed to assess the likelihood of human effects at environmental exposure levels (ATSDR, 1992d).

ATSDR has declined to develop oral MRLs for acute, intermediate, or chronic duration oral exposure due to the lack of data on sensitive endpoints for these durations. They note the need for a behavioral study because it appears to be a sensitive endpoint. Other studies that are needed include a multigeneration study, which includes a measurement of reproductive system toxicity, immunological effects—particularly with developmental exposures, pharmacokinetic studies, and studies to determine methods for reducing body burden (ATSDR, 1992d).

5.3.1.11 Summary of EPA Levels of Concern—

Chronic Toxicity	6×10^{-5} mg/kg/d
Carcinogenicity	1.3 per mg/kg/d.

5.3.1.12 Major Sources—

ATSDR (1992d), HSDB (1993), IRIS (1993).

5.3.2 DDT, DDE, DDD

5.3.2.1 Background—

DDT is an organochlorine pesticide that has not been marketed in the United States since 1972 but is ubiquitous due to its widespread use in previous decades and its relatively long half-life. DDT's close structural analogs, DDE and DDD, are metabolites of DDT and have also been formulated as pesticides in the past (Hayes, 1982). DDT is very widely distributed; it has been found in seals in Finland and reptiles in the Everglades (HSDB, 1993). The NHANES II study (National Human Monitoring Program of the EPA) detected DDE, a metabolite of DDT, in 99 percent of the 12- to 74- year-old study subjects (living in the Northeast, Midwest, and South). The median level was 11.8 ppb in blood serum (HSDB, 1993).

Although some use of DDT continues throughout the tropics, it remains of human health concern in the United States primarily due to its presence in water, soil, and food (Hayes, 1982). Because individuals are typically exposed to a mixture of DDE, DDT, and DDD and their degradation and metabolic products (ATSDR, 1992c), the sum of the 4,4'- and 2,4'- isomers of DDT, DDE, and DDD should be

considered in the development of fish consumption limits for this group of chemicals (U.S. EPA, 1993a).

5.3.2.2 Pharmacokinetics—

DDT and its analogs are stored in fat, liver, kidney, and brain tissue; trace amounts can be found in all tissues (Hayes, 1982). DDE is stored more readily than DDT (Hayes, 1982). DDT is eliminated through first-order reduction to DDD and, to a lesser extent, to DDE. The DDD is converted to more water-soluble bis (p-chlorophenyl)-acetic acid, with a biological half-life of 1 year. DDE is eliminated much more slowly, with a biological half-life of 8 years. Because elimination occurs slowly, ongoing exposure may lead to an increase in the body burden over time.

5.3.2.3 Acute Toxicity—

See the listing of usual effects associated with organochlorine exposure in Appendix C. The low effect dose for severe effects (acute pulmonary edema) in infants has been reported to be 150 mg/kg. In adults, behavioral effects were noted at 5 to 6 mg/kg and seizures at 16 mg/kg (HSDB, 1993).

Evidence from acute exposure studies of dogs indicates that DDT may sensitize the myocardium to epinephrine. This was observed for both injected epinephrine and epinephrine released by the adrenal glands during a seizure, and resulted in ventricular fibrillation (Hayes, 1982). DDT may concurrently act on the CNS, in a manner similar to that of other halogenated hydrocarbons, to increase the likelihood of fibrillation (Hayes, 1982). Chronic exposure to 10 mg/kg/d did not produce increased incidence of arrhythmias in rats or rabbits (Hayes, 1982).

DDD is considered less toxic than DDT in animals. Symptoms develop more slowly and have a longer duration with DDD than with DDT exposure. Lethargy is more significant and convulsions are less common than with DDT exposure (HSDB, 1993).

5.3.2.4 Chronic Toxicity—

Extensive research has been conducted on chronic and subchronic exposure effects of DDT in animals and in humans working with DDT. These studies have primarily focused on carcinogenic effects, which are discussed in Section 5.3.2.7. Studies have also identified liver damage, and there is limited evidence that DDT may cause leukocytosis and decreased hemoglobin level (Hayes, 1982).

Immunological effects have been associated with exposure to DDT. Exposure to DDT at 2.63 mg/kg/d for 10 days resulted in immunological effects in rabbits. With 31 days of exposure at 1 mg/kg/d in rats, a decrease in the number of mast cells was observed. A relatively recent 8-week study in rabbits found decreases in germinal centers of the spleen and atrophy of the thymus (categorized as serious effects by ATSDR) at 0.18 mg/kg/d. Other effects were observed at higher doses.

No studies were provided on immunological effects following chronic exposure (ATSDR, 1992c).

DDT may have reproductive system toxicity. It appears to bind to uterine tissue and have estrogenic activity (Hayes, 1982). Metabolites of DDT bind to the cytoplasmic receptor for estrogen, which may result in inadvertent hormonal response (agonist) or depress normal hormonal balance (antagonist). Either may result in reproductive abnormalities (HSDB, 1993). The animal studies of the reproductive system have yielded mixed results. Chronic animal studies have identified LOELs that range over orders of magnitude. Serious adverse effects (decreased fertility and decreased litter size) have been observed at 0.35 and 0.91 mg/kg/d, respectively, in subchronic animal studies. Edema of the testes occurred at 2 mg/kg/d in a rat study. NOELs are not available for these studies. Other studies have identified NOELs ranging from 2.4 to 10 mg/kg/d with severe effects at 12 mg/kg/d (increased maternal and offspring death) (ATSDR, 1992c). Significant reproductive (function and lactation) abnormalities have also been observed at higher doses (83 mg/kg/d in rats and at 33.2 mg/kg/d in mice). Function abnormalities have also been observed in dogs (Hayes, 1982).

IRIS lists an oral RfD of 5×10^{-4} mg/kg/d based on liver effects with a NOEL of 0.05 mg/kg/d from a 27-week rat feeding study conducted in 1950. Uncertainty factors of 10 each for inter- and intraspecies variability were used; however, the usual factor of 10 for a less-than-lifetime study was not applied “because of the corroborating chronic study in the data base” (IRIS, 1993). The corroborating study was conducted in 1948.

More recent studies of the immunological and reproductive systems (noted above) suggest a LOEL from subchronic studies in the range of 0.18 to 0.35. There are numerous studies supporting the occurrence of both types of effects, and both are serious in nature. An alternative estimated exposure limit could be calculated using these more recent data. The most sensitive endpoint appears to be immunological effects observed in the rabbit study (noted above). This study had a LOEL of 0.18 mg/kg/d. The standard uncertainty factors used in this calculation would typically take into consideration inter- and intraspecies variability, the use of a LOEL rather than a NOAEL, and the use of a less-than-lifetime study.

5.3.2.5 Developmental Toxicity—

DDT causes embryotoxicity and fetotoxicity but not teratogenicity in experimental animals (ATSDR, 1992c). Studies indicate that estrogen-like effects on the developing reproductive system occur (ATSDR, 1992c). This also occurs with chronic exposure as discussed in Section 5.3.2.4. Rabbits exposed to 1 mg/kg/d early in gestation had decreased fetal brain, kidney, and body weights (ATSDR, 1992c). Prenatal exposure in mice at 1 mg/kg on 3 intermittent days resulted in abnormal gonad development and decreased fertility in offspring, which was especially evident in females (Hayes, 1982).

A three-generation rat reproduction study found increased offspring mortality at all dose levels with a LOEL of 0.2 mg/kg/d. Three other reproduction studies found no effects at much higher dose levels (IRIS, 1993). Effects on the urogenital system were found with 8 days' prenatal exposure in mice. Behavioral effects in mice exposed prenatally for 7 days were noted at 17.5 mg/kg/d (HSDB, 1993).

Prenatal 1-day exposure of rabbits to DDT resulted in an abnormal persistence of preimplantation proteins in the yolk sac fluid. The results suggest that DDT caused a cessation of growth and development before implantation or during later uterine development. The authors suggest that damage can be repaired but may result in offspring with prenatal growth retardation in the absence of gross abnormalities (HSDB, 1993). Most dosages tested for these effects have been relatively high. Postnatal exposure of rats for 21 days to 21 mg/kg (the only dose tested) resulted in adverse effects on lactation and growth.

In dogs, placental passage of DDT to the fetus has been demonstrated. This was confirmed in mice. Primary targets include the liver, adipose tissue, and intestine. Rabbit blastocysts (a very early stage of development) contained a significant amount of DDT shortly after administration to the mother (HSDB, 1993).

Biomagnification in human milk has been observed. In lactating women with an intake of 5×10^{-4} mg/kg/d of DDT, the milk contained 0.08 ppm. This was calculated to result in infant doses of 0.0112 mg/kg/d, which is approximately 20 times the dosage to the mothers (HSDB, 1993).

DDT is suspected of causing spontaneous abortion in humans and cattle (Hayes, 1982). It is not known whether this is related to the reproductive system toxicity of DDT (see Section 5.3.2.4) or developmental toxicity. The average concentration of DDE in the blood of premature babies (weighing <2,500 g) was significantly greater than those of higher birth weight infants (HSDB, 1993). The relationship between spontaneous abortion, premature delivery, and maternal exposure and body burden requires clarification.

ATSDR reports that a recent developmental study in mice found behavioral abnormalities in offspring exposed prenatally at 0.5 mg/kg/d. Latent effects were observed following cessation of exposure, and subsequent tissue evaluation found structural/function alterations in the brain. Effects reported include an abnormal increase in activity and probable altered learning ability. The effects occurred at levels approximately 50-fold lower than those that were noted in adults and did not cease when dosing was discontinued or when tissue levels had decreased. This information was used to support the hypothesis of permanent structural changes in the brain. The results of this study were used by ATSDR to calculate an acute exposure MRL of 5×10^{-4} mg/kg/d using standard uncertainty factors of 10 each for inter- and intraspecies variability and the use of a LOEL rather than a NOEL (ATSDR, 1992c). This MRL is based upon a sensitive endpoint with structural and functional toxicity correlations and should be considered for use as an exposure limit for developmental effects of DDT, DDE, and DDD. Readers may elect to

consider the ATSDR MRL for developmental toxicity. The MRL is the same value as the current IRIS RfD (as listed under Section 5.3.2.4).

DDT accumulates in body tissue; consequently, exposure occurring prior to pregnancy can contribute to the overall maternal body burden and result in exposure to the developing individual. As a result , it is necessary to reduce exposure to children and females with childbearing potential to reduce overall body burden. If a female has been exposed to DDT, even if exposure is reduced during pregnancy, the outcome of that pregnancy may be affected, depending on the timing and extent of prior exposure.

5.3.2.6 Mutagenicity—

"Genotoxicity studies in human systems strongly suggest that DDT may cause chromosomal damage" (ATSDR, 1992c). This is supported by in vitro and in vivo studies in animals (ATSDR, 1992c) and in some bacterial assays (HSDB, 1993). There are multiple positive assays including human lymphocytes, human leukocytes, human fibroblasts, an oncogenic transformation, and unscheduled DNA synthesis in rats in multiple studies (ATSDR 1992c; HSDB, 1993).

5.3.2.7 Carcinogenicity—

DDE, DDT, and DDD are all considered probable human carcinogens (B2) based on animal studies, with cancer potencies of 0.24, 0.34, and 0.34 per mg/kg/d, respectively (IRIS, 1993). Liver tumors were associated with each chemical. It is noted in the IRIS file that 24 of the 25 carcinogenicity assays of DDT have yielded positive results. The occupational studies of workers exposed to DDT are of insufficient duration to assess carcinogenicity (IRIS, 1993). Elevated leukemia incidence, particularly chronic lymphocytic leukemia, was noted in two studies of workers. Lung cancer has also been implicated in one study. Bone marrow cells in experimental animals have also been affected by exposure, including an increase in chromosomal fragments in the cells (HSDB, 1993).

It is recommended that the total concentration of the 2,4'- and 4,4'-isomer of DDT and its metabolites, DDE and DDD, be evaluated as a group using the cancer potency of 0.34 per mg/kg/d (U.S. EPA, 1993a). In addition, the EPA Carcinogenicity Assessment Group has recommended that this value be used for combinations of dicofol with the above three compounds (U.S. EPA, 1993a).

5.3.2.8 Special Susceptibilities—

Based on the information obtained from a recent developmental study that found neurotoxicity and structural brain alterations at relatively low exposures (approximately 50-fold less than in adults), children may be at greater risk from DDT exposure than adults.

The results of the cardiac toxicity studies are not consistent; however, it is safest to assume that exposure to DDT or its analogs **may** pose a risk for individuals with

cardiac disease, at exposure levels estimated to be safe for the general population (Hayes, 1982).

Individuals exposed to DDT may metabolize some drugs more rapidly than the general population (HSDB, 1993) (see also Appendix C). For example, increased phenobarbital metabolism resulting from an increased body burden of DDT (10 µg) led to a 25 percent decrease in effectiveness of the drug in experimental animals. The toxicity of chloroform was enhanced by the addition of DDT to the diet due to its capacity as a microsomal stimulator (HSDB, 1993). Alterations in the metabolism of drugs, xenobiotics, and steroid hormones may result from DDT exposure due to DDT's induction of the hepatic mixed-function oxidase system at relatively low doses (HSDB, 1993). Individuals who use medications that involve the mixed function oxidase system directly (MFO inhibitors) or through metabolic processes may be at risk for alteration of the drugs' efficacy and/or timing if they are exposed to DDT. Information is not available for this document on the specific relationships between various pharmaceuticals and DDT/DDE/DDD body burdens or intakes. This type of information merits further investigation.

ATSDR notes that persons with diseases of the nervous system or liver may be particularly susceptible to the effects of DDT (ATSDR, 1992c). Based on information discussed above regarding biomagnification in milk, nursing infants may also be at greater risk due to their increased exposure.

5.3.2.9 Interactive Effects—

As discussed in Section 5.3.2.8, DDT exposure may alter the response to drugs, xenobiotics, and endogenous steroid hormones. (See the discussion of organochlorine effects related to induction of the mixed function oxidase system in Appendix C.) DDT is reported to promote some tumorigenic agents and antagonize others. The actions may be related to the induction of microsomal enzymes (ATSDR, 1992c).

5.3.2.10 Critical Data Gaps—

IRIS notes the lack of a NOEL for reproductive effects and a relatively short duration for the critical study on which the RfD is based. No intermediate or chronic oral MRLs were calculated by ATSDR because of the lack of a NOEL and the seriousness of the LOEL in significant studies (ATSDR, 1992c).

Information was not located for this document on the specific relationships between various pharmaceuticals and DDT/DDE/DDD body burdens or intakes. Information on the relationship between pre- and postnatal exposure and behavioral effects and maternal exposure and milk concentrations is also needed.

An interagency group of researchers from NTP, ATSDR, and EPA have identified the following data gaps: pharmacokinetic data; animal studies on respiratory, cardiovascular, GI, hematological, musculoskeletal, and dermal/ocular effects; the significance of subtle biochemical changes such as the induction of microsomal

enzymes in the liver and the decreases in biogenic amines in the nervous system in humans; an epidemiological study in humans of estrogen-sensitive cancers including endometrial, ovarian, uterine, and breast cancer; reproductive system toxicity; developmental toxicity; a multiple assay battery for immunotoxicity; subtle neurological effects in humans; and mechanisms of neurotoxicity in the neonate (ATSDR, 1992c).

5.3.2.11 Summary of EPA Levels of Concern—

These values should be used for the sum of the 4,4'- and 2,4'- isomers of DDT, DDE, and DDD.

Chronic Toxicity	5×10^{-4} mg/kg/d
Carcinogenicity	0.34 per mg/kg/d.

5.3.2.12 Major Sources—

ATSDR (1992c), Hayes (1982), HSDB (1993), IRIS (1993).

5.3.3 Dicofol (Kelthane)

5.3.3.1 Background—

Dicofol is an organochlorine pesticide that is structurally similar to DDT and is frequently contaminated with isomers of DDT, DDE, and DDD (U.S. EPA, 1993a). Dicofol is considered a DDT analog based on its structure and activity (Hayes and Laws, 1991). In the past, dicofol often contained 9 to 15 percent DDT and its analogs. In 1989 EPA required that these contaminants constitute less than 0.1 percent of dicofol (HSDB, 1993).

5.3.3.2 Pharmacokinetics—

Very few data were located regarding the pharmacokinetics of dicofol. Due to its structural similarity to DDT, it may be assumed to have some of the same properties. Data regarding metabolites are not consistent. The mechanism of action is hypothesized to be inhibition of the ATPase associated with oxidative phosphorylation and cation transport in the plasma membranes (HSDB, 1993).

5.3.3.3 Acute Toxicity—

See the listing of usual effects associated with organochlorine exposure in Appendix C. The acute oral LD_{50}s for dicofol from animal studies ranged from 640 to 1,810 mg/kg (U.S. EPA, 1993g).

5.3.3.4 Chronic Toxicity—

No IRIS file was located for this chemical. OPP lists an RfD of 0.001 mg/kg/d based on a NOEL of 1 mg/kg/d in a 2-year rat feeding study (no information was

located on the critical effect). Uncertainty factors totaling 1,000 were applied (U.S. EPA, 1992d).

The liver is a target organ for dicofol both for systemic and carcinogenic effects. Studies have also reported thyroid hypertrophy in rats at 25 mg/kg/d. A NOEL of 0.9 mg/kg/d was identified in a recent study of liver toxicity, based on gross and microscopic pathology and enzyme alterations, in a 1-year dog study (U.S. EPA, 1993g). This study would yield an estimated exposure limit within approximately 1 order of magnitude of the RfD listed above.

Due to the limited information available for this review on the dose-response dynamics for dicofol, it is recommended that the OPP value of 0.001 mg/kg/d be used for chronic systemic toxicity.

5.3.3.5 Developmental Toxicity—

Two three-generation reproductive studies in mice and rats both identified a NOEL of 1.5 mg/kg/d with effects at 3.375 mg/kg/d noted as reduced litter size, reduced body weight, and reduced offspring survival (U.S. EPA, 1993g). The reviewed data did not contain information regarding underlying mechanisms of fetal or neonatal toxicity. Additional uncertainty arises because of the limited information available in the database regarding the study outcomes. They are gross measures of toxicity and do not provide any indication of the level of exposure at which organ toxicity that led to death was occurring. Consequently, an estimated exposure limit for developmental effects cannot be estimated with precision. If these studies were used, the standard uncertainty factors employed in the calculation would typically take into account consideration of inter- and intraspecies variability. An additional modifying factor for the limited information available in the database could also be used.

As with the other organochlorines, it is anticipated that dicofol can accumulate in body tissue; consequently, exposure occurring prior to pregnancy can contribute to the overall maternal body burden and result in exposure to the developing individual. As a result, it is necessary to reduce exposure to children and females with childbearing potential to reduce overall body burden. If exposure is reduced during pregnancy but has occurred prior to pregnancy, the pregnancy outcome may be affected, depending on the timing and extent of prior exposure.

5.3.3.6 Mutagenicity—

Studies of dicofol in human lymphoid cells in vitro were positive with an incidence of events 13 times that of controls. It induced sister chromatid exchange with activation. Other mutagenicity studies in bacteria have yielded negative results (HSDB, 1993).

5.3.3.7 Carcinogenicity—

Dicofol has been classified as a B2 and C carcinogen by offices within EPA. OPP lists the potency value as 0.44 per mg/kg/d (U.S. EPA, 1992c). The EPA Carcinogenicity Assessment Group (CAG) has recommended that 0.34 per mg/kg/d be used for combinations of dicofol with DDT, DDE, and DDD (U.S. EPA, 1993a). The value of 0.44 per mg/kg/d was used to develop fish consumption limits listed in Section 4 for carcinogenic effects.

5.3.3.8 Special Susceptibilities—

Individuals taking medications that involve the mixed function oxidase system may need to alter their dosages when exposure to dicofol is occurring at significant levels. No specific information was available on the critical dosage for interaction. See Appendix C for more information on this topic.

Individuals with liver disease and children exposed prenatally may also be at risk based on the toxicity information reviewed.

5.3.3.9 Interactive Effects—

As with other organochlorine pesticides, microsomal enzyme induction occurs and may cause interactions with other chemicals. See a discussion of this in Appendix C. No additional data were located.

5.3.3.10 Critical Data Gaps—

Information is lacking on neurotoxicity endpoints for chronic and developmental toxicity. Based on data available on other organochlorines, this type of toxicity commonly occurs and may be a sensitive endpoint that could serve as a useful basis for chronic or developmental toxicity exposure limits. The reviewed data did not contain information regarding underlying mechanisms of fetal lethality. A sensitive measure of developmental toxicity is necessary to generate a protective exposure limit. Clarification is also needed regarding the carcinogenic nature of dicofol.

5.3.3.11 Summary of EPA Levels of Concern—

Chronic Toxicity	1.0×10^{-3} mg/kg/d
Carcinogenicity	0.44 per mg/kg/d for dicofol alone
	0.34 per mg/kg/d in combination with DDT, DDE, DDD.

5.3.3.12 Major Sources—

HSDB (1993), U.S. EPA (1993g).

5.3.4 Dieldrin

5.3.4.1 Background—

Dieldrin is an organochlorine pesticide that was phased out between 1974 and 1987. It continues to be detected nationwide due to its relatively long half-life. Dieldrin is also a product of aldrin metabolism (ATSDR, 1991a).

5.3.4.2 Pharmacokinetics—

Dieldrin is absorbed from the GI tract and transported via the hepatic portal vein and the lymphatic system. It is found shortly after exposure in the liver, blood, stomach, and duodenum. Dieldrin is lipophilic and is ultimately stored primarily in fat and tissues with lipid components (e.g., brain) (ATSDR, 1991a).

In human dosing studies at 0.0001 to 0.003 mg/kg/d over 2 years, the time to achieve equilibrium was approximately 15 months. A dynamic equilibrium was theorized with the average ratio of the concentration in adipose tissue to blood of 156. Cessation of dosing led to decreases in blood levels following first-order kinetics with a half-life ranging from 141 to 592 days and an average of 369 days (ATSDR, 1991a).

The metabolism of dieldrin is described in detail in ATSDR (1991a). Sex and species differences have been reported in the metabolism and tissue distribution of dieldrin based on chronic exposure studies and toxicokinetic studies in animals. Males appear to metabolize and excrete dieldrin more rapidly than females (ATSDR, 1991a).

A correlation between exposure and dieldrin levels in human breast milk has been established. Placental transfer of dieldrin has been observed in women, with higher concentrations measured in fetal blood than in maternal blood (ATSDR, 1991a).

5.3.4.3 Acute Toxicity—

See the listing of usual effects associated with organochlorine exposure in Appendix C. Additional effects include: possible hematological effects in humans (pancytopenia and thrombocytopenia, immunohemolytic anemia) (ATSDR, 1991a). An estimated human lethal dose is 65 mg/kg (HSDB, 1993).

5.3.4.4 Chronic Toxicity—

IRIS provides an RfD of 5×10^{-5} mg/kg/d based on a NOAEL of 0.005 mg/kg/d from a 1969 2-year rat feeding study that found liver lesions. Uncertainty factors of 10 each for inter- and intraspecies variability were applied (IRIS, 1993). Liver toxicity has been observed in multiple animal studies and in human acute exposure episodes. Adaptive changes (e.g., liver enlargement) have been

observed at 0.00035 mg/kg/d in a subchronic rat study. ATSDR has calculated an MRL that is equal to the RfD listed in IRIS (ATSDR, 1991a).

Although the critical effect in the IRIS study was liver lesions, it was noted that, at the next highest dose (0.05 mg/kg/d), “all animals became irritable and exhibited tremors and occasional convulsions” (IRIS, 1993). There was no listing of additional neurobehavioral studies in the IRIS file. As an organochlorine pesticide, it is expected that dieldrin is a CNS toxicant. This is supported by acute toxicity effects of dieldrin and the neurotoxicity studies listed below.

Other effects associated with dieldrin exposure include: arterial degeneration in rats with a chronic exposure to 0.016 mg/kg/d, hematological disorders in experimental animals at 0.25 and 1 mg/kg/d, musculoskeletal pathology at 0.015 mg/kg/d in a chronic rat study, kidney degeneration and other changes at 0.125 mg/kg/d in chronic animal studies in multiple species, hypertension in humans (exposure level unknown), and multiple deficits in immune system function in multiple studies (ATSDR, 1991a). Increased susceptibility to tumor cells was observed in a subchronic mouse study (dose not specified in material reviewed) (HSDB, 1993).

Neurological effects of dieldrin have been observed in experimental animals and in humans exposed acutely and chronically. Wheat mixed with aldrin and lindane was consumed for 6 to 12 months by a small human population. Effects were attributed to aldrin (converted to dieldrin via metabolism) because the wheat had been mixed with lindane in previous years without adverse effect. A variety of CNS disorders were observed, and abnormal EEGs were noted. Some symptoms (myoclonic jerks, memory loss, irritability) continued for at least 1 year after cessation of exposure. A child is believed to have developed mild mental retardation as a result of exposure. Quantitative exposure information was not available in the data reviewed (ATSDR, 1991a).

Neurotoxicity has been observed in humans with chronic inhalation and dermal exposures (ATSDR, 1991a). Chronic exposure of pesticide applicators to dieldrin led to idiopathic epilepsy, which ceased when exposure was terminated (HSDB, 1993). Dermal and inhalation exposure were the likely routes of exposure. No exposure quantitation was available.

A 1967 study of human exposure effects over 18 months at levels up to 0.003 mg/kg/d identified no effects on the CNS (as measured by EEG), peripheral nerve activity, or muscle activity (ATSDR, 1991a).

Animal studies have identified neurological effects including behavioral disorders and learning deficits at doses of 0.1 to 0.25 mg/kg/d in subchronic and chronic studies. Higher doses produced more dramatic effects (e.g., convulsions, tremors). Cerebral edema and degeneration were found with chronic exposure of rats to 0.016 mg/kg/d (ATSDR, 1991a). Neural lesions (cerebral, cerebellar, brainstem, and vascular) were observed in chronically exposed rats at 0.004 mg/kg/d (HSDB, 1993).

With the exception of the neurological study discussed directly above, the information reviewed regarding neurotoxicity indicates that the IRIS RfD would be protective against adverse effects, using standard assumptions for the development of an exposure limit. Although the neurological rat study cited above noted effects at 0.004 mg/kg/d, the human study of exposure over an 18-month period at 0.003 mg/kg/d found no effects on the CNS based on various sensitive measures. Taking the results of the human study under consideration, it appears, based on the information reviewed, that the IRIS RfD provides adequate protection against neurological effects in the human population.

Dieldrin causes reproductive system disorders in animals and one study suggests that it may cause adverse effects in humans. In a study evaluating the blood and placental levels of organochlorines associated with premature labor or spontaneous abortions in women, positive results were obtained for aldrin. Most exposed subjects had multiple chemical exposures; consequently, interpretation of study results is difficult (ATSDR, 1991a). See also notes regarding estrogenic activity in Section 5.3.4.7.

Studies of reproductive effects in animals indicate that exposure to dieldrin may cause a number of adverse effects. Dieldrin exposure causes changes in the levels of serum luteinizing hormone (LH) in females and gonadotropin in males. Dieldrin interferes with the binding of dihydrotestosterone to male sex hormone receptors (HSDB, 1993). These three hormones are critical to normal reproductive function. A mouse study found decreased fertility with exposure to 1.3 mg/kg/d in females and 0.5 mg/kg/d in males. Another study found no effects at much higher exposure levels. Adverse reproductive effects in dogs exposed at an LEL of 0.15 mg/kg/d for 14 months prior to mating included increased stillbirth rates, delayed estrus, reduced libido, and a lack of mammary function and development. Maternal behavior was studied in mice exposed for 4 weeks prior to delivery until weaning at 1.95 mg/kg/d. Exposed maternal animals violently shook the pups, ultimately killing them; others neglected their litters (ATSDR, 1991a).

Based on the information reviewed regarding reproductive toxicity, it appears that the IRIS RfD would be protective against adverse effects, using standard assumptions and uncertainty factors for calculating an estimated exposure limit.

5.3.4.5 Developmental Toxicity—

IRIS provides limited information regarding the developmental toxicity of dieldrin. A NOEL of 6 mg/kg/d was obtained from a mouse teratology study with exposure occurring from the 7th to 16th day of gestation. Fetotoxicity (decreased numbers of caudal ossification centers and an increased incidence of extra ribs) was observed with an LEL of 6 mg/kg/d. This study was not considered in development of the IRIS file because 41 percent of the maternal fatalities occurred at the LEL dose (IRIS, 1993). An RfD based on developmental effects is not provided in IRIS.

A variety of effects in multiple organ systems have been observed in experimental animals exposed prenatally to dieldrin. Skeletal anomalies and malformations

(e.g., cleft palate, webbed foot, open eyes, extra ribs) were identified at relatively large doses (LEL of 3 mg/kg/d) (ATSDR, 1991a).

Abnormalities of the CNS, eye, and ear were noted with a TD Lo (similar to a LOEL) of 30.6 mg/kg prenatal exposure, and craniofacial abnormalities were observed at a single prenatal dose of 15 mg/kg/d (HSDB, 1993). Liver damage has been observed in experimental animals at dosages as low as 0.016 mg/kg/d (ATSDR, 1991a). Note that liver lesions are the basis for the chronic toxicity RfD derived from a study of adult animals, as reported in IRIS (IRIS, 1993). A multigeneration study in mice found histological changes in liver, kidney, lungs, and brain tissues in the first and second generation offspring at an LEL of 3 ppm (0.075 mg/kg/d) (HSDB, 1993).

Multiple studies have reported increased postnatal mortality following prenatal exposure to dieldrin. Studies in dogs, rats, and mice have found LELs of 0.125 to 0.65 mg/kg/d associated with high mortality in offspring in the absence of increased maternal mortality. Studies designed to evaluate the underlying causes of mortality suggest that cardiac glycogen depletion, leading to cardiac failure, may be causal (ATSDR, 1991a).

Neural lesions in prenatally exposed rats were found at an LEL of 0.004 mg/kg/d. Effects included cerebral edema, internal and external hydrocephalus, and focal neuronal degeneration. Postnatal exposure of rats from day 5 of gestation to 70 days of age resulted in increased learning ability at 3.5×10^{-4} mg/kg/d (the only dose tested). ATSDR has cautioned that “interpretation of the results is difficult because the significance of improved performance in behavioral paradigms is unknown, and the study is limited because only one dose of dieldrin was tested” (ATSDR, 1991a). In a rat multigeneration study, a TD Lo of 0.014 mg/kg/d with behavioral effects was observed (HSDB, 1993).

Dieldrin is known to accumulate in human milk. In one study of 102 samples in the United States, 91.2 percent of the samples contained measurable levels of dieldrin, with a mean concentration of 0.062 ppm lipid basis. Another U.S. study found 80 percent of the 1,436 samples were positive with a range of 0.16 to 0.44 ppm milk fat (HSDB, 1993). This indicates that lactation may provide a significant dietary source in infants with mothers who have been exposed to dieldrin. As discussed above, studies in humans also determined that dieldrin can pass through the placenta and is found in fetal blood.

Neurotoxicity appears to be a relatively sensitive endpoint for developmental toxicity. The association of neurotoxic effects with dieldrin exposure is supported by the observation of neurological effects in human populations exposed to dieldrin. The study noted in the paragraph above that identified neural lesions associated with prenatal exposure provided an LEL of 0.004 mg/kg/d provides the most sensitive developmental toxicity measure of those reviewed. If the LEL from this study were used to calculate an estimated exposure limit for developmental effects, the standard uncertainty factors would typically take into consideration inter- and intraspecies variability and the use of an LEL rather than a NOAEL.

As with the other organochlorines, it is anticipated that dieldrin can accumulate in body tissue; consequently, exposure occurring prior to pregnancy can contribute to the overall maternal body burden and result in exposure to the developing individual. As a result, it is necessary to reduce exposure to children and females with childbearing potential to reduce overall body burden. If a female has been exposed to dieldrin, even if exposure is reduced during pregnancy, the outcome of that pregnancy may be affected, depending on the timing and extent of prior exposure.

5.3.4.6 Mutagenicity—

There is limited information on the mutagenicity of dieldrin. Positive in vivo studies have found an increased incidence in the number of abnormal metaphases in dividing spermatocytes and in univalents. Dominant lethal assays (in vivo) have yielded mixed results. in vitro assays have also yielded mixed results. Positive results have been obtained in cultured human lung cells and mouse bone marrow cells (both found increases in chromosome aberrations) and sister chromatid exchange (SCE) assays.

Dieldrin may not act directly on DNA; however, it may act by depressing transfer RNA activity, increasing unscheduled DNA synthesis, and inhibiting metabolic cooperation and gap junctional intercellular communication, according to mechanistic studies. The inhibition of gap junctional communication may be responsible for carcinogenic activity through depressing the cells' ability to control excess proliferation. This inhibition has been correlated with strains and species in which dieldrin has been shown to be carcinogenic. This type of activity is considered promotion rather than initiation of tumors (ATSDR, 1991a).

5.3.4.7 Carcinogenicity—

Dieldrin is classified as a probable human carcinogen (B2) by EPA based on oral studies in animals. The oral cancer slope factor is 16 per mg/kg/d. Liver carcinoma was identified in the animal studies. The geometric mean of 13 data sets (with a range of a factor of 8) were used to develop the cancer potency (IRIS, 1992). This value was used to calculate fish consumption limits listed in Section 4 for carcinogenic effects.

A variety of tumor types have been observed in animal studies including pulmonary, lymphoid, thyroid, and adrenal (ATSDR, 1991a). ATSDR has concluded that dieldrin is probably a tumor promotor, based on genotoxicity and mechanistic studies reviewed (ATSDR, 1991a). Dieldrin has recently been observed to have estrogenic effects on human breast cancer estrogen-sensitive cells (Soto et al., 1994). Xenoestrogens have been hypothesized to have a role in human breast cancer (Davis et al., 1993). In addition to potential carcinogenic effects, dieldrin may also cause disruption of the endocrine system due to its estrogenic activity (Soto et al., 1994).

5.3.4.8 Special Susceptibilities—

ATSDR has identified the following populations as unusually susceptible: very young children with immature hepatic detoxification systems, persons with impaired liver function, and persons with impaired immune function (ATSDR, 1991a). Based on the toxicity data reviewed above, individuals with the following diseases or disorders may also be at increased risk: hypertension, hematological disorders, musculoskeletal diseases, neurological diseases, and kidney disease.

The data also indicate that prenatal exposure may generate risks to children at relatively low levels of exposure. Postnatal exposure, especially via lactation, may also be a significant concern.

See also a discussion of susceptibilities associated with pharmaceutical use in Appendix C.

5.3.4.9 Interactive Effects—

See the discussion of organochlorine effects related to induction of the mixed function oxidase system in Appendix C. In cows, dieldrin exposure increased the toxicity of diazinon; greater depression in blood cholinesterase activity occurred, leading to severe clinical signs (HSDB, 1993).

MIXTOX has reported inhibition between dieldrin and hexachlorobenzene in rats exposed orally via food. Studies have also reported additive effects (MIXTOX, 1992).

5.3.4.10 Critical Data Gaps—

A joint team of scientists from EPA, NTP, and ATSDR have identified the following study data gaps: animal carcinogenicity, genotoxicity in vivo and in vitro, reproductive system toxicity, developmental toxicity, especially mechanisms of postnatal mortality and teratogenesis, immunotoxicity, neurotoxicity focusing on sensitive endpoints, and pharmacokinetics (ATSDR, 1991a).

5.3.4.11 Summary of EPA Levels of Concern—

Chronic Toxicity	5×10^{-5} mg/kg/d
Carcinogenicity	16 per mg/kg/d.

5.3.4.12 Major Sources—

ATSDR (1991a), HSDB (1993), IRIS (1993).

5.3.5 Endosulfan I, II

5.3.5.1 Background—

Endosulfan is an organochlorine pesticide comprised of stereoisomers designated I and II, which have similar toxicities (U.S. EPA, 1993a). Endosulfan I and II are referred to collectively as endosulfan; discussions refer to both isomers unless otherwise noted. Endosulfan has been found widely in food samples, including one of 10 fruit and fruit juice samples for infants at a mean concentration of 0.01 ppb (HSDB, 1993).

5.3.5.2 Pharmacokinetics—

Endosulfan is absorbed through the GI tract and is distributed throughout the body. Endosulfan is metabolized to lipophilic compounds and both the parent and metabolites are found initially primarily in the kidney and liver and fatty tissue, with distribution to other organs occurring over time. Endosulfan can induce microsomal enzyme activity and is a nonspecific inducer of drug metabolism. In sheep, approximately 1 percent of a single dose was recovered in milk. Females may accumulate endosulfan more readily than males according to animal studies. This may be causal in the higher toxicity seen in females (see Acute Toxicity below) (ATSDR, 1993b).

5.3.5.3 Acute Toxicity—

Endosulfan has a high acute toxicity to humans, with an estimated lethal dose of 50 to 500 mg/kg. Multiple animal studies found females much more sensitive to exposure than males (e.g., acute oral LD_{50} of 9.5 in females and 40.4 in males) (U.S. EPA, 1992c). See the listing of usual effects associated with organochlorine exposure in Appendix C. In addition to those listed in Appendix C, bluing of the skin (IRIS, 1993), hematopoietic system damage and anemia, possibly damage to red blood cell membranes, cardiac toxicity, and immunotoxicity have been noted (ATSDR, 1993b).

5.3.5.4 Chronic Toxicity—

IRIS previously provided an RfD of 5×10^{-5} mg/kg/d for endosulfan based on a LOAEL of 0.15 mg/kg/d from a two-generation rat reproduction study that identified kidney toxicity. Uncertainty factors totaling 3,000 were applied (IRIS, 1992). The RfD was withdrawn in December 1992, and a new RfD summary is under development (IRIS, 1993). The Office of Pesticide Programs has recently reevaluated this chemical and calculated an RfD of 6×10^{-3} mg/kg/d (U.S. EPA, 1996b).

ATSDR developed intermediate exposure duration (14-365 days) and chronic duration MRLs of 0.002 mg/kg/d for both intermediate and chronic exposures. These MRLs are based on immunotoxicity and hepatotoxicity, respectively (ATSDR, 1993b).

Other chronic effects of endosulfan noted in studies include: blood vessel aneurysms at 0.65 mg/kg/d, neurological effects at 1.71 mg/kg/d, damage to the hematopoietic system at 3.75 mg/kg/d, and elevated hemoglobin levels at 0.1 mg/kg/d (U.S. EPA, 1993i). It appears that the old IRIS RfD would be protective against the effects noted, based on current risk assessment methods.

Two National Cancer Institute studies have identified the following effects: interstitial fibrosis or acute tubular necrosis of the kidney, atrophy of the testes, polyarteritis, parathyroid hyperplasia, osteitis fibrosis of the bone, and abscesses of the lung. The kidney effects led to most deaths (dosages were not listed in the database) (HSDB, 1993). A number of additional studies have also found damage to the male reproductive system associated with exposure to endosulfan (e.g., testicular necrosis, aspermatogenesis, degeneration of seminiferous tubule epithelium) (ATSDR, 1993b). (See discussion of estrogenic activity under Carcinogenicity below.)

A neurological study in rats exposed at 3 mg/kg/d for 30 days found increased aggressive behavior at both doses along with a significant increase in serotonin binding in the frontal cortical membranes that may have been due to an increase in the affinity of the serotonin receptors (HSDB, 1993). This effect has negative implications for human behavior. Abnormal increases in behavior in prenatally exposed animals have also been noted for other organochlorine pesticides (see Appendix C on organochlorines); however, this level of mechanistic detail has not been located for other organochlorines in the reviews conducted for this document.

5.3.5.5 Developmental Toxicity—

Multiple teratogenic effects were associated with endosulfan exposure in a rat developmental toxicity study including webbed forelimb, clubbed hind limbs, hypoplastic aortic arch, edema and lordosis, increased incidence of small 4th and unossified 5th sternebrae, and decreased pup size and weight. An increased incidence of misaligned vertebrae was observed at all dose levels with an LEL of 0.66 mg/kg/d (U.S. EPA, 1993i).

Other developmental studies have yielded a variety of results that are often inconsistent (e.g., two separate studies found unspecified effects at the lowest dose tested of 5 mg/kg/d in one study and no effects at the highest dose tested of 1.8 mg/kg/d in another study). A range-finding single-generation reproductive study found increased liver weights at the lowest dose tested of 2.5 mg/kg/d. A two-generation reproductive study found increased pituitary and uterine weights at 3.75 mg/kg/d and a NOEL of 0.75 mg/kg/d. Kidney discoloration, which was originally attributed to hematopoietic damage at all doses, has been reevaluated and is now considered by OPP to be part of the elimination process rather than an adverse effect (U.S. EPA, 1993i). It is not clear why significant differences in effects were noted in multiple recent rat studies (i.e., the first and last studies discussed in this paragraph).

Postnatal exposure of rats for 5 weeks at 1 mg/kg/d resulted in aggressive behavior and increased serotonin binding. This persisted after the dosing stopped. The study authors concluded that the developing study subjects had a greater sensitivity to endosulfan than adults (ATSDR, 1993b).

In the absence of more complete information, a conservative approach is recommended for calculation of an estimated limit for developmental effects, due to the severity of effects observed in the teratogenicity study with a LOEL of 0.66 mg/kg/d (listed first above). If this study, which appears to be the most sensitive, were used to calculate an estimated exposure limit, the uncertainty factors used in this calculation would typically take into consideration inter- and intraspecies variability and the use of an LEL rather than a NOEL.

As with the other organochlorines, it is anticipated that endosulfan can accumulate in body tissue; consequently, exposure occurring prior to pregnancy can contribute to the overall maternal body burden and result in exposure to the developing individual. As a result, it is necessary to reduce exposure to children and females with childbearing potential to reduce overall body burden. If a female has been exposed to endosulfan, even if exposure is reduced during pregnancy, the outcome of that pregnancy may be affected, depending on the timing and extent of prior exposure.

5.3.5.6 Mutagenicity—

Results of mutagenicity assays of endosulfan are mixed, with multiple positive and negative studies (ATSDR, 1993b; HSDB, 1993; IRIS, 1993). Endosulfan has resulted in an increase in the percentage of aberrant colonies and the frequency of gene convertants and revertants in yeast and was genetically effective without activation. Longer duration of exposure increased effects (HSDB, 1993). In vivo assays have found chromosomal aberrations and gene mutations in mice (ATSDR, 1993b).

5.3.5.7 Carcinogenicity—

Insufficient information is available to determine the carcinogenic status of endosulfan I and II. The carcinogenic assays have yielded mixed results, with carcinomas, sarcomas, and lymphosarcomas identified at increased incidences in some studies. ATSDR has concluded that the available animal study data were negative or inconclusive (ATSDR, 1993b). Endosulfan has recently been observed to have estrogenic effects on human breast cancer estrogen-sensitive cells (Soto et al., 1994). Xenoestrogens have been hypothesized to have a role in human breast cancer (Davis et al., 1993). In addition to potential carcinogenic effects, endosulfan may also cause disruption of the endocrine system due to its estrogenic activity (Soto et al., 1994).

5.3.5.8 Special Susceptibilities—

As noted above, multiple animal studies found females much more sensitive to endosulfan exposure than males, some by nearly 1 order of magnitude (U.S. EPA, 1992c). However, toxicity studies indicate that the male reproductive system is a target organ for endosulfan toxicity (ATSDR, 1993b).

Animal neurobehavioral study results indicate that the developing test animals had a greater sensitivity to endosulfan than adults based on neurotransmitter patterns and behavioral effects observed (ATSDR, 1993b). This may indicate that children are at greater risk for neurotoxicity than adults. ATSDR has noted that:

> There is evidence from animal studies indicating that unborn and neonates may be more susceptible to the toxic effects of endosulfan because hepatic detoxification systems are immature and therefore unable to metabolize xenobiotic substances efficiently. (ATSDR, 1993b)

Additional groups who may be at greater risk from endosulfan exposure include those with: liver, kidney, immunological, or blood diseases; compromised immune systems such as AIDS patients, infants, and elderly people; hematologic disorders; seizure disorders; and low protein diets (see below) (ATSDR, 1993b). See also a discussion of susceptibilities associated with pharmaceutical use in Appendix C.

5.3.5.9 Interactive Effects—

Human anecdotal information suggests that endosulfan may act synergistically with alcohol (ATSDR, 1993b). In laboratory animals, moderate protein deprivation doubled the toxicity of endosulfan (Hayes and Laws, 1991).

Pentobarbital and endosulfan have demonstrated an interactive effect that is probably related to microsomal enzyme activity. Endosulfan induces the mixed function oxidase system (ATSDR, 1993b). Vitamin A inhibited the endosulfan-induced activity of the mixed function oxidase system (ATSDR, 1993b). See a discussion of organochlorine effects related to induction of the mixed function oxidase system in Appendix C.

5.3.5.10 Critical Data Gaps—

The increased susceptibility of females to endosulfan should be studied to determine the underlying cause, evaluate whether the effect occurs with chronic exposure, and identify a numerical modifier to adjust toxicity estimates and exposure recommendations so that they provide adequate protection for females.

Additional data are needed on the teratogenic and neurobehavioral effects during development resulting from endosulfan exposure. Current data do not provide a consistent picture nor do they explain underlying mechanisms of toxicity; thus, they

somewhat compromise the determination of an exposure limit for developmental effects.

A joint team of scientists from ATSDR, NTP, and EPA have identified the following data gaps: acute oral exposure studies, mechanisms of anemia-inducing effects, reproductive system toxicity and related performance, developmental toxicity studies, mechanisms of immunotoxicity, sensitive neurological function and histological studies for long-term exposures, epidemiological studies, pharmacokinetics of intermediate and chronic duration exposures, and studies evaluating mechanisms underlying the differences in male and female toxicity. No ongoing studies were identified for endosulfan (ATSDR, 1993b).

5.3.5.11 Summary of EPA Levels of Concern—

Chronic Toxicity	6×10^{-3} mg/kg/d
Carcinogenicity	Insufficient data to determine carcinogenic status.

5.3.5.12 Major Sources—

ATSDR (1993b), HSDB (1993), IRIS (1993), U.S. EPA (1993i).

5.3.6 Endrin

5.3.6.1 Background—

Endrin is an organochlorine pesticide whose registration was canceled in 1984 (U.S. EPA, 1993a).

5.3.6.2 Pharmacokinetics—

Endrin, like the other organochlorine pesticides, is lipophilic. It bioaccumulates in fat and probably brain tissue and can cross the placenta. Endrin is metabolized via oxidation of the methylene bridge. Metabolic products are probably more toxic than endrin and the toxic entity has been hypothesized to be 12-ketoendrin. In humans, this compound is excreted directly in urine and feces (ATSDR, 1990c).

5.3.6.3 Acute Toxicity—

Endrin has a high acute toxicity (IRIS, 1993). See the listing of usual effects associated with organochlorine exposure in Appendix C. Blood pressure elevation has also been noted (IRIS, 1993). The primary target of endrin is the central nervous system (ATSDR, 1990c).

5.3.6.4 Chronic Toxicity—

IRIS provides an RfD of 2×10^{-4} mg/kg/d based on a NOAEL of 0.025 mg/kg/d from a 1969 chronic exposure dog study that identified histological lesions in the liver and convulsions in study subjects exposed at the LEL of 0.05 mg/kg/d.

Uncertainty factors of 10 each for inter- and intraspecies variability were applied (IRIS, 1993). ATSDR used the same study and safety factors to calculate an MRL equal to the IRIS RfD (ATSDR, 1990c).

OPP tox one-liners list a 1959 2-year dog feeding study with a LOAEL of 0.015 mg/kg/d based on hypersensitivity in the neck and shoulder area. Increased erythropoiesis was noted at 0.125 mg/kg/d (U.S. EPA, 1993m). The LOAEL of 0.015 is within 1 order of magnitude of the LEL identified in the critical IRIS study. The IRIS value was used to calculate fish consumption limits for chronic exposure effects listed in Section 4.

5.3.6.5 Developmental Toxicity—

No developmental effects were listed in the IRIS file for endrin (IRIS, 1993). ATSDR listed a number of prenatal exposure studies that identified structural abnormalities and neurotoxicity associated with endrin exposure. Structural abnormalities have been observed in mice and hamsters exposed to endrin. These include fused ribs and cleft palate at 5 mg/kg/d for 3 prenatal days and webbed foot and open eye effects in hamster fetuses prenatally exposed for 1 day. Meningeocephaloceles in hamsters were caused by a single prenatal exposure “above” 1.5 mg/kg and fused ribs “above” 5 mg/kg in hamsters. In mice, a single prenatal exposure to 2.5 mg/kg caused an increase in open eyes. Exencephaly and fused ribs were seen with one exposure at 9 mg/kg endrin. A rat study reported no developmental effects with exposure to 0.45 mg/kg/d (it was not clear if behavioral effects were evaluated) (ATSDR, 1990c). The variation in effects is probably due in part to the different prenatal periods during which exposure occurred (see ATSDR, 1990c). Reproductive outcome was adversely affected in hamsters exposed to 1.5 mg/kg/d with decreased survival of pups (16 percent mortality). The underlying cause was not discussed (ATSDR, 1990c).

Nervous system effects are a significant concern with organochlorine exposure. In hamsters, abnormally increased pup activity in hamsters was observed with 1.5 mg/kg prenatal exposures for 9 days. The NOEL for these behavioral effects was 0.075 mg/kg/d (ATSDR, 1990c). In rats, increased activity was seen with prenatal exposure to 0.3 mg/kg/d (ATSDR, 1990c). Abnormally increased activity has been observed for other organochlorine pesticides (see DDT) and has been associated with probable altered learning ability and permanent structural changes to the brain.

Both structural skeletal changes and neurological abnormalities are significant developmental effects associated with endrin. Decreased survival, while a significant effect, is not usually a sensitive measure of toxicity. The behavioral effects observed with a NOEL of 0.075 mg/kg/d (discussed above) are recommended for estimation of an exposure limit for developmental toxicity due to their greater sensitivity. The uncertainty factors used in this calculation would typically take into consideration inter- and intraspecies variability.

As noted in the pharmacokinetics section above, endrin can accumulate in body tissue; consequently, exposure occurring prior to pregnancy can contribute to the overall maternal body burden and result in exposure to the developing individual. As a result, it is necessary to reduce exposure to children and females with childbearing potential to reduce overall body burden. If exposure is reduced during pregnancy but has occurred prior to pregnancy, the pregnancy outcome may be affected, depending on the timing and extent of prior exposure.

5.3.6.6 Mutagenicity—

In vitro assays of endrin suggest that it is not genotoxic. There were no in vivo assay results located (ATSDR, 1990c).

5.3.6.7 Carcinogenicity—

Insufficient information is available to determine the carcinogenic status of endrin. EPA has classified this as a Group D carcinogen (insufficient information available). Some studies have yielded positive results and some studies that reported negative results were considered to be inadequate (IRIS, 1993). Tumors have been noted in the adrenal glands, pituitary glands, liver, mammary gland, uterus, and thyroid in various studies and multiple species (IRIS, 1993). Endrin is structurally related to a number of chemicals that are carcinogenic in test animals, including chlordane, aldrin, dieldrin, heptachlor, and chlorendic acid (IRIS, 1993). Because endrin has been classified as a Group D carcinogen, no cancer potency has been listed by EPA.

5.3.6.8 Special Susceptibilities—

ATSDR has reported that children may be more sensitive to acute endrin exposure than adults, based on effects observed in children during a poisoning incident. Children appeared more susceptible to neurotoxic effects and have exhibited convulsions. This is supported by results observed in experimental animals where young rats were more susceptible than adults (ATSDR, 1990c).

In addition, the skeletal and behavioral abnormalities associated with endrin exposure in experimental animals indicate that prenatal exposure may generate special risks.

Based on animal studies, females may be more susceptible than males to endrin-induced toxicity (ATSDR, 1990c).

See also a discussion of susceptibilities associated with pharmaceutical use in Appendix C.

5.3.6.9 Interactive Effects—

See a discussion of organochlorine effects related to induction of the mixed function oxidase system in Appendix C. Dietary pretreatment with endrin

potentiates the hepatotoxicity of carbon tetrachloride. MIXTOX has reported synergism between endrin and chlordane in mice with gavage exposure (MIXTOX, 1992).

5.3.6.10 Critical Data Gaps—

A joint team of researchers from ATSDR, NTP, and EPA have identified the following data gaps: human responses to acute, intermediate (14 to 365 days), and chronic exposures; subchronic reproductive tests in various species; immunotoxicity studies of animals and humans; human dosimetry studies; pharmacokinetic studies; and studies of interspecies differences in metabolism and toxicity (ATSDR, 1990c).

5.3.6.11 Summary of EPA Levels of Concern—

Chronic Toxicity	3×10^{-4} mg/kg/d
Carcinogenicity	Insufficient data to determine carcinogenic status.

5.3.6.12 Major Sources—

ATSDR (1990c), IRIS (1993), U.S. EPA, 1993m.

5.3.7 Heptachlor Epoxide

5.3.7.1 Background—

Heptachlor epoxide is a breakdown product of the organochlorine pesticide heptachlor and chlordane and is a contaminant of both products. It is more toxic than either parent compound (ATSDR, 1993c). Although most uses of heptachlor were suspended in 1978 and chlordane was removed from the market in 1988 (U.S. EPA, 1993j), heptachlor epoxide continues to be a widespread contaminant due to its relatively long half-life.

5.3.7.2 Pharmacokinetics—

Based upon animal and limited human data, heptachlor epoxide is absorbed through the GI tract and is found primarily in the liver, bone marrow, brain, and fat, although it is distributed widely to other tissues as well. It is stored primarily in fat. Fetal blood levels were approximately four times those measured in women. Levels in human milk range from zero to 0.46 ppm (ATSDR, 1993c).

Heptachlor epoxide has a very long half-life, particularly in adipose tissue. Human tissue levels have correlated well to age, with 97 percent of North Texas residents tested (ages 41 to 60) having measurable levels. Based on the Texas study, heptachlor epoxide tissue levels have not decreased appreciably since the 1960s (ATSDR, 1993c).

5.3.7.3 Acute Toxicity—

See the listing of usual effects associated with organochlorine exposure in Appendix C. The LD_{50}s for heptachlor range from 40 to 162 mg/kg in rodents (ATSDR, 1993c).

5.3.7.4 Chronic Toxicity—

IRIS provides an RfD of 1.3×10^{-5} mg/kg/d based on an LEL of 0.0125 mg/kg/d from a 60-week dog feeding study reported in 1958. The critical effect was increased liver-to-body-weight ratios in both males and females at the lowest dose tested. Uncertainty factors of 10 each were applied for inter- and intraspecies variability and the use of an LEL rather than a NOEL (IRIS, 1993). No additional uncertainty factors were applied for the use of a less-than-lifetime study. The principal study is of low quality and there is a low confidence in the RfD (IRIS, 1993).

Animal studies have identified the following effects associated with heptachlor (and subsequently heptachlor epoxide via metabolism) or heptachlor epoxide directly: elevated bilirubin and white blood cell count, increased serum creatinine phosphokinase levels suggestive of muscle damage, muscle spasms secondary to CNS stimulation, adrenal gland pathology, and neurological disorders (ATSDR, 1993c).

Significant changes in EEG patterns were found in female adult rats exposed to 1 and 5 mg/kg/d for three generations (ATSDR, 1993c).

A study of reproductive system toxicity with males and females dosed at 0.25 mg/kg/d prior to and during gestation found a significantly decreased pregnancy rate among exposed animals. Based on specific fertility tests, it was determined that males were most likely affected and that sperm were probably killed (ATSDR, 1993c). Another reproductive system toxicity study with doses at and above 0.075 mg/kg/d resulted in the failure of animals to reproduce. There were serious deficiencies in this study (ATSDR, 1993c).

5.3.7.5 Developmental Toxicity—

A 1973 two-generation dog reproductive study identified a NOEL of 0.025 mg/kg/d with an LEL of 0.075 mg/kg/d with liver lesions in pups. Other studies with higher LELs based on a lethality endpoint are listed in the IRIS file. They were not used in this evaluation due to insufficient information. The IRIS file notes data gaps as rat and rabbit teratology studies (IRIS, 1993).

Exposure of adult rats to 6 mg/kg/d caused lens cataracts in 22 percent of the adults, 6 to 8 percent of the F1 generation offspring, and 6 percent of the F2 generation offspring. A rat study with exposure to 0.25 mg/kg/d occurring 60 days prior to mating and during gestation resulted in severely reduced pup survival (15 percent) at 21 days postpartum (ATSDR, 1993c). This is not a useful LOEL due to the severity of effects observed at the lowest dose tested.

A human study conducted in Hawaii was not considered adequate due to many study design deficiencies (ATSDR, 1993c). In another epidemiological study of women who had premature deliveries, significantly higher levels of heptachlor epoxide and other organochlorine pesticides were detected in sera (ATSDR, 1993c).

There are limited data on which to base an estimated exposure limit for developmental effects. The NOEL in the two-generation study is not based on sensitive endpoints and is only a factor of 3 removed from the LEL. The developmental toxicity database is insufficient for heptachlor epoxide (per the IRIS file). Consequently, the application of an uncertainty factor for the insufficiency of the database may be necessary. The dog study, with a NOEL of 0.025 mg/kg/d, can be used to calculate an exposure limit for developmental effects. The standard uncertainty factors used in this calculation would typically take into consideration inter- and intraspecies variability and a database factor.

As noted in Section 5.3.7.2, heptachlor can accumulate in body tissue; consequently, exposure occurring prior to pregnancy can contribute to the overall maternal body burden and result in exposure to the developing individual. As a result, it is necessary to reduce exposure to children and females with childbearing potential to reduce overall body burden. If exposure is reduced during pregnancy but has occurred prior to pregnancy, the pregnancy outcome may be affected, depending on the timing and extent of prior exposure.

5.3.7.6 Mutagenicity—

Mixed results have been obtained in mutagenicity assays of heptachlor epoxide.

5.3.7.7 Carcinogenicity—

Heptachlor epoxide is classified as a probable human carcinogen (B2) by EPA based on oral studies in animals. The oral cancer slope factor is 9.1 per mg/kg/d. This value is based on the geometric mean of several studies that identified liver carcinomas (IRIS, 1993). Six structurally related compounds have produced tumors in mice and rats: chlordane, aldrin, dieldrin, heptachlor, and chlorendic acid (IRIS, 1993).

Statistically significant increases in adenomas and carcinomas of the thyroid were found in female rats. Some researchers discounted the results due to the low incidence and known variability in the control population (ATSDR, 1993c).

Heptachlor (and consequently heptachlor epoxide) exposures have been associated with cerebral gliosarcoma in children exposed prenatally. Multiple chromosomal abnormalities were also identified in the tumor cells. It was not determined whether the effects were caused by environmental or familial factors (ATSDR, 1993c).

5.3.7.8 Special Susceptibilities—

Based on the toxicity data reviewed above, individuals with diseases or disorders of the following systems may be at greater risk than the general population: liver, hematopoietic, musculoskeletal, neurological, and adrenal gland. ATSDR has noted that preadolescent children may be more susceptible due to their greater rate of glutathionine turnover (ATSDR, 1993c). In addition, children exposed prenatally may be at higher risk, based on the results of developmental toxicity studies.

See also a discussion of susceptibilities associated with pharmaceutical use in Appendix C.

5.3.7.9 Interactive Effects—

See a discussion of organochlorine effects related to induction of the mixed function oxidase system in Appendix C.

5.3.7.10 Critical Data Gaps—

The IRIS file notes data gaps as rat and rabbit teratology studies (IRIS, 1993). The OPP notes the same data gaps (U.S. EPA, 1992c). A joint team of scientists from EPA, NTP, and ATSDR have identified the following data gaps: a model to describe the relationship between tissue and blood levels and exposure in humans, chronic oral exposure effects in humans, epidemiological and in vivo animal genotoxicity studies, developmental and reproductive toxicity studies and neurotoxicity and immunotoxicity studies in animals, and pharmacokinetic studies (ATSDR, 1993c).

5.3.7.11 Summary of EPA Levels of Concern—

Chronic Toxicity	1.3×10^{-5} mg/kg/d
Carcinogenicity	9.1 per mg/kg/d.

5.3.7.12 Major Sources—

ATSDR (1993c), IRIS (1993).

5.3.8 Hexachlorobenzene

5.3.8.1 Background—

Hexachlorobenzene is a byproduct of manufacturing and has been used as a fungicide seed protectant in the past. It exists as a solid at ambient temperatures, and in aquatic environments is found in higher quantities in sediment than water due to its low solubility (ATSDR, 1990a).

5.3.8.2 Pharmacokinetics—

Hexachlorobenzene is persistent in the body, accumulating preferentially in fat and tissues with a high lipid content, due to its lipophilic nature. It is found in human breast milk (ATSDR, 1990a), which may be a significant route of exposure for young children.

5.3.8.3 Acute Exposure—

Acute exposure studies in animals indicate a relatively low acute toxicity with LD_{50}s between 1,700 and 4,000 mg/kg (ATSDR, 1990a). Based on animal studies, the following systems are adversely affected following acute exposure: liver, kidney, hematological, and dermal (ATSDR, 1990a). See also the discussion of organochlorine pesticides in Appendix C.

5.3.8.4 Chronic Toxicity—

Hexachlorobenzene exposure of a large number of people in Turkey occurred between 1955 and 1959 due to consumption of contaminated grain. No precise exposure estimates are available for children or adults in this episode; it is likely that exposures occurred over a continuum, with some individuals consuming much higher levels than others. Researchers have estimated relatively low exposure levels occurred over several years as a result of consumption (50 to 200 mg/d). These exposure levels are approximately 0.7 to 2.9 mg/kg/d for a 70-kg individual. ATSDR has emphasized that the exposure estimates are unverified (ATSDR, 1990a).

The following effects have been associated with hexachlorobenzene exposure in individuals exposed chronically via contaminated bread (Turkey): shortening of the digits due to osteoporosis, painless arthritis, decreased uroporphyrin synthase levels, muscle weakness, rigidity and sensory shading, thyroid enlargement, and histopathological changes in the liver often accompanied by skin lesions (ATSDR, 1990a). These effects were also observed in numerous animal studies. (See discussion under Section 5.3.8.5 also.)

The hepatic system appears to be the most sensitive systemic endpoint for hexachlorobenzene exposure, based on animal studies, with a NOAEL of 0.08 mg/kg/d in a lifetime rat study. This has been converted by ATSDR to an MRL of 8×10^{-4} mg/kg/d using uncertainty factors of 10 each for inter- and intraspecies variability (ATSDR, 1990a). This value is also the IRIS RfD for chronic systemic toxicity (IRIS, 1993). Numerous other studies identified NOAELs in the same numerical range. The IRIS file notes that the sensitive endpoint of porphyria, which is an effect noted in exposed human populations, was not evaluated in the critical animal study (IRIS, 1993). It is not possible, based on the current data, to determine whether the RfD will be protective against that effect.

The oral RfD of 8×10^{-4} mg/kg/d developed by IRIS and ATSDR was used to calculate the fish consumption limits listed in Section 4 for chronic exposure

toxicity. For a summary of the chronic systemic toxicity data, the reader is referred to the *Toxicity Profile for Hexachlorobenzene* (ATSDR, 1990a).

5.3.8.5 Developmental Toxicity—

Lactational exposure to hexachlorobenzene is of significant concern, based on the rapid transfer of the chemical through breast milk and effects observed in children of exposed mothers. In a study of nursing infants, the infants had blood levels of hexachlorobenzene two to five times that of their mothers, as well as higher tissue levels. A study of monkeys found that the concentration in milk was 17 times higher than that in maternal serum (ATSDR, 1990a). Young children (under 1 year) of lactating mothers who were exposed via contaminated bread had an extremely high mortality rate. Skin lesions, weakness, and convulsions were reported in these infants. Although adults were also adversely affected, children appeared to be at higher risk. The maternal exposure was roughly estimated to be 0.7 to 2.9 mg/kg/d (ATSDR, 1990a).

Among slightly older children (average age of 7), exposure via food resulted in the development of small or atrophied hands and fingers, short stature, pinched faces, osteoporosis in the hands, and other arthritic changes. Exposure was estimated to be approximately 0.7 to 2.9 mg/kg/d (ATSDR, 1990a).

It is known that hexachlorobenzene can cross the human placenta; however, no data were available on effects resulting from prenatal exposure in humans. Very limited information is available on experimental animals. Cleft palate and kidney abnormalities were observed in one study in a single litter and fetus at 100 mg/kg/d (ATSDR, 1990a). In another study, the survivability of prenatally exposed rats was significantly reduced at 2 mg/kg/d (estimated from ppm with conversion factor of 0.05 mg/kg per 1 ppm diet for rats). Death was attributed to maternal body burden and cumulative lactational exposure (ATSDR, 1990a). Alterations in immune function levels were reported in pre- and postnatally exposed rats at 4 mg/kg (ATSDR, 1990a).

For purposes of quantitatively estimating an exposure limit, it is of concern that prenatal and lactational exposure of humans at levels roughly estimated to be 0.7 to 2.9 mg/kg/d (maternal) induced serious structural changes in children and increased mortality. Due to the poor quality of data supporting the exposure estimates for the human exposure episode in Turkey and, more critically, the lack of a no-effect level, it would be desirable to obtain a developmental study with a more reliable exposure estimate. However, there do not appear to be such studies currently available. Much higher exposure levels were required to cause structural changes in experimental animals and the experimental results have not been duplicated. These data suggest that humans may be more susceptible than the animals studied.

In the absence of better data, the human study data from Turkey can be used to calculate an estimated exposure limit for developmental effects. The standard uncertainty factors used in this calculation would typically take into consideration

intraspecies variability, the use of a LOAEL rather than a NOAEL, and the overall inadequacy of the database. An additional modifying factor may be applied for the poor quality of the exposure data and the severity of the effects noted at the LOAEL. Due to the incomplete nature of the database and the other inadequacies noted above, there would not be a high level of confidence in exposure limits calculated from the current developmental toxicity database.

As noted above, hexachlorobenzene accumulates in body tissue; consequently, exposure occurring prior to pregnancy can contribute to the overall maternal body burden and result in exposure to the developing individual. As a result, it is necessary to reduce exposure to children and women with childbearing potential to reduce overall body burden. If a female has been exposed to hexachlorobenzene, even if exposure is reduced during pregnancy, the outcome of that pregnancy may be affected, depending on the timing and extent of prior exposure.

5.3.8.6 Mutagenicity—

The results of mutagenicity studies on hexachlorobenzene are mixed (IRIS, 1993). Hexachlorobenzene was negative in dominant lethal studies (in vivo) at doses from 60 to 221 mg/kg (ATSDR, 1990a).

5.3.8.7 Carcinogenicity—

Carcinogenic assays of hexachlorobenzene in animals have identified an increased incidence of multiple tumor types including hepatomas, hemangioendotheliomas, liver, and thyroid tumors in multiple species. EPA developed a cancer potency of 1.6 mg/kg/d based on liver carcinoma in female rats exposed via diet. In support of this value, cancer potencies were calculated for 14 different data sets; the results were within 1 order of magnitude. Hexachlorobenzene is classified as a probable human carcinogen (B2) based on the results of animal studies (IRIS, 1993). The IRIS cancer potency of 1.6 per mg/kg/d was used to calculate the fish consumption limits listed in Section 4 for carcinogenic effects.

Human studies have not yet yielded useful results. Followup studies of exposure victims in Turkey have not identified cancers in the 25- and 20- to 30-year exposure cohorts; however, ATSDR suggests that the enlarged thyroids noted in members of these groups have not been sufficiently investigated (ATSDR, 1990a). It should also be noted that most cancers have multiple-decade latency periods and often occur in the later part of life. Consequently, it will not be possible to assess the carcinogenic impact of exposures in Turkey for some time.

5.3.8.8 Special Susceptibilities—

ATSDR has concluded that young children are susceptible to hexachlorobenzene exposure based on human poisoning episodes. Exposure led to permanent debilitating effects. Both human and animal data suggest that the risk of exposure to nursing infants may be greater than the risk to their mothers (ATSDR, 1990a).

Based on the toxicity data reviewed above, individuals with liver disease may be at greater risk than the general population.

See also a discussion of susceptibilities associated with pharmaceutical use in Appendix C.

5.3.8.9 Interactive Effects—

Hexachlorobenzene induces microsomal enzymes. See Appendix C for a discussion of associated effects. Pentachlorophenol increases the porphyrinogenic effects of hexachlorobenzene. Hexachlorobenzene potentiated the thymic atrophy and body weight loss caused by 2,3,7,8-TCDD. A 50 percent food deprivation increased liver hypertrophy and microsomal enzyme induction by hexachlorobenzene (ATSDR, 1990a).

5.3.8.10 Critical Data Gaps—

A joint team of scientists from EPA, NTP, and ATSDR have identified the study following data gaps: human carcinogenicity, in vivo and in vitro genotoxicity, animal reproductive toxicity, animal developmental toxicity, immunotoxicity studies in humans, and pharmacokinetics (ATSDR, 1990a). Information is needed to develop a model that can be used to estimate the relationship between maternal intake, human milk concentration, and adverse effects in infants.

5.3.8.11 Summary of EPA Levels of Concern—

Chronic Toxicity	8×10^{-4} mg/kg/d
Carcinogenicity	1.6 per mg/kg/d.

5.3.8.12 Major Sources—

ATSDR (1990a), IRIS (1993).

5.3.9 Lindane (γ-hexachlorocyclohexane)

5.3.9.1 Background—

Lindane is an organochlorine pesticide that is comprised of isomers of hexachlorocyclohexane, with the γ isomer constituting the major (>99 percent) component. There appears to be some difference in toxicity of the various hexachlorocyclohexane isomers (U.S. EPA, 1993a). The following data assume that lindane can be defined as the γ isomer.

5.3.9.2 Pharmacokinetics—

Lindane is readily absorbed by the GI tract following oral exposure. Distribution is primarily to the adipose tissue but also to the brain, kidney, muscle, spleen, adrenal glands, heart, lungs, blood, and other organs. It is excreted primarily

through urine as chlorophenols. The epoxide metabolite may be responsible for carcinogenic and mutagenic effects (ATSDR, 1992b).

Male exposure to lindane through the environment results in accumulation in testes and semen in addition to the tissues listed above (ATSDR, 1992b). See also a discussion in Section 5.3.9.5 of the accumulation of lindane by pregnant women.

5.3.9.3 Acute Toxicity—

See the listing of usual effects associated with organochlorine exposure in Appendix C. The estimated human lethal dose is 125 mg/kg (HSDB, 1993). Occupational and accidental exposures in humans have resulted in headaches, vertigo, abnormal EEG patterns, seizures, and convulsions. Death has occurred primarily in children. ATSDR recommends an acute (14 days' exposure or less) exposure MRL of 0.003 mg/kg/d based on neurotoxic effects in rats (ATSDR, 1992b).

5.3.9.4 Chronic Toxicity—

IRIS provides an RfD of 3×10^{-4} mg/kg/d based on a NOAEL of 0.33 mg/kg/d from a subchronic rat study that found liver and kidney toxicity. Uncertainty factors of 10 each for inter- and intraspecies variability and the use of a less-than-lifetime study were applied (IRIS, 1993). A recently completed 2-year study is under evaluation and may provide additional information regarding toxicity (U.S. EPA, 1993k). Liver damage has been observed in animal studies (U.S. EPA, 1993k). Immune system effects have been observed in humans exposed via inhalation and in orally dosed animals. A 5-week study in rabbits found immunosuppression at 1 mg/kg/d (ATSDR, 1992b).

Most observed effects in humans exposed accidentally to lindane are neurological. Behavioral effects have also been noted in many studies on experimental animals, and at relatively high levels seizures were reported. More subtle behavioral effects were noted at an LEL of 2.5 mg/kg/d with 40 days of exposure in rats. No NOEL was reported (ATSDR, 1992b).

Two recent reproductive studies in rats found adverse effects on the male reproductive system. In a 7-week study, decreased sperm counts were noted at 50 mg/kg/d and, in a 180-day study, seminiferous tubular degeneration was noted at 6 mg/kg/d with a NOEL of 3 mg/kg/d. An older study had identified the same effects at 64.6 mg/kg/d in a 3-month study. Experimental data indicate that the female reproductive system may also be altered by lindane exposure. A study of rats found uterine, cervical, and vaginal biochemical changes at 20 mg/kg/d in a 30-day study. Antiestrogenic effects were found at 20 mg/kg/d in female rats in a 15-week study with a NOEL of 5 mg/kg/d. This action was also found in two other recent studies (ATSDR, 1992b). Based on current risk assessment methods, it appears that the current IRIS RfD for chronic effects is protective against reproductive system toxicity. However, the effects in both the male and female reproductive systems have been evaluated only in short-term studies. Evaluation

of these effects in a longer-term study, and identification of the underlying mechanisms of toxicity, would provide information needed for a more complete evaluation of toxicity and dose-response dynamics.

It is not clear whether the IRIS RfD is protective against neurotoxic effects because the study of behavioral effects that resulted in an LEL of 2.5 mg/kg/d was a short-term study and no NOEL was identified. Neurotoxic effects have been reported widely in human poisoning incidents and among occupationally exposed individuals. Consequently, it is of significant interest for human toxicity. Additional information is needed to determine whether the current RfD is protective against neurotoxic effects.

5.3.9.5 Developmental Toxicity—

Two developmental toxicity studies in rats and rabbits both identified a NOEL of 10 mg/kg (no effects were described for higher doses). A three-generation rat study found no adverse reproductive effects at 5 mg/kg/d, the highest dose tested (U.S. EPA, 1993k). A recent mouse study found increased resorptions at 5 mg/kg/d. Studies in rats and mice have found increased incidence of extra ribs at 5 to 20 mg/kg/d (ATSDR, 1992b). There are multiple studies showing pre- and postimplantation fetotoxicity and skeletal abnormalities resulting from prenatal exposure at higher doses (HSDB, 1993).

Lindane accumulates in the fatty tissue of pregnant (and nonpregnant) women where it can be transferred to the fetus through the placenta and to infants through breast milk. Human milk concentrations are approximately five to seven times greater than maternal blood levels. Concentrations in maternal blood are proportional to the length of time over which exposure occurred, with older women having higher blood levels. During pregnancy, the lindane concentration in blood from fetal tissue, uterine muscle, placenta, and amniotic fluid was higher than levels in maternal adipose tissue, and blood serum levels increased during delivery (ATSDR, 1992b). There is little information on the effects of exposure during lactation. One study (dose unspecified) in rats indicated that exposure during gestation and lactation did not cause developmental effects; however, this is not consistent with other studies that found effects associated with gestational exposure.

Based on what is known regarding the transfer of lindane into human milk, nursing infants must be considered at some risk if their mothers have been exposed to significant amounts of lindane (lindane is a lipid-seeking chemical). Additional information is needed to characterize the relationship between maternal intake, body burden (blood or adipose levels), milk concentrations, and adverse effects.

Multiple studies have reported that lindane exposure (as measured by body tissue level of lindane) is associated with premature labor and spontaneous abortions.

The causal relationship has not been established for this action (ATSDR, 1992b); however, the reproductive system effects discussed in Section 5.3.9.4 (biochemical changes in uterine, cervical, and vaginal tissues and antiestrogenic effects) may be involved.

Information was not located on developmental neurotoxicity, which may be an expected effect of lindane based on the toxicity of other organochlorines. Based on the limited data available, the most appropriate studies for use in calculating an estimated exposure limit for developmental effects are the rat and mouse studies that identified the development of extra ribs and fetal resorptions, respectively, at an LEL of 5 mg/kg/d. Resorptions, which usually arise from early fetal death, are typically the result of toxicity to the fetus. Information on the nature of that toxicity was not available in the data reviewed for this document. In this case, the resorptions could have arisen from systemic toxicity, or there may have been hormonal effects that also jeopardized maintenance of pregnancy, as indicated by the reproductive system toxicity data (see Section 5.3.9.4).

In estimating an exposure limit for lindane, the uncertainty generated by the potential for lactation exposure must also be considered. It may be advisable to use an additional modifying factor to account for lack of critical information in the database regarding the actual dose at which toxic effects occurred (those more sensitive than lethality), the potential for premature labor and spontaneous abortions, and the potential for increased exposure via lactation. For purposes of calculating an exposure limit, if the rat and mouse LEL were used, standard uncertainty factors would typically take into consideration inter- and intraspecies variability and the use of an LEL rather than a NOEL. A modifying factor may also be applied. (See also Sections 5.3.9.8 and 5.3.9.9.)

As noted above, lindane accumulates in body tissue; consequently, exposure occurring prior to pregnancy can contribute to the overall maternal body burden and result in exposure to the developing individual. As a result, it is necessary to reduce exposure to children and women with childbearing potential to reduce overall body burden. If exposure is reduced during pregnancy but has occurred prior to pregnancy, the pregnancy outcome may be affected, depending on the timing and extent of prior exposure.

5.3.9.6 Mutagenicity—

In animals, ingestion of technical-grade hexachlorocyclohexane induced dominant lethal mutations in mice. Studies found that lindane binds to mouse liver DNA at a low rate. Based on a review of genotoxicity studies, ATSDR concluded that lindane “has some genotoxic potential, but the evidence for this is not conclusive” (ATSDR, 1992b).

5.3.9.7 Carcinogenicity—

Lindane has been classified as a probable/possible carcinogen (B2/C) based on liver tumors in animals. The cancer potency is 1.3 per mg/kg/d (HEAST, 1992). In

addition to tumors identified in experimental animals, human study data indicate that this chemical may cause aplastic anemia (U.S. EPA, 1993a). Lindane is currently under review by EPA. Lindane's related isomers, alpha and beta hexachlorocyclohexane, are also classified as probable human carcinogens and have cancer potencies similar to that of lindane. The cancer potency obtained from the HEAST tables was used to calculate the fish consumption limits listed in Section 4 for carcinogenic effects.

5.3.9.8 Special Susceptibilities—

ATSDR has recommended that pregnant and/or lactating women should not be exposed to lindane. The potential for premature labor and spontaneous abortion is noted (ATSDR, 1992b). People with epilepsy, cerebrovascular accidents, or head injuries who have lower thresholds for convulsions may be at greater risk of lindane-induced CNS toxicity and seizures. Also, individuals with protein-deficient diets, liver or kidney disease, or immunodeficiencies may be at greater risk from lindane exposure than the general population (ATSDR, 1992b).

Children may also be at greater risk from lindane exposure because of the immaturity of their immune and nervous systems. ATSDR has cautioned that:

> Infants and children are especially susceptible to immunosuppression because their immune systems do not reach maturity until 10 to 12 years of age (ATSDR, 1990b).

See also a discussion of susceptibilities associated with pharmaceutical use in Appendix C.

5.3.9.9 Interactive Effects—

See a discussion of organochlorine effects related to induction of the mixed function oxidase system in Appendix C.

High- and low-protein diets and vitamin A and C deficiencies increased the toxicity of lindane in experimental animals. Vitamin A supplements decreased toxicity. Cadmium inhibited the metabolism of lindane. Combined cadmium and lindane exposure caused significant embryotoxic and teratogenic effects in rats at dosages that caused no effects when administered alone. Exposure to the α, β, and δ hexachlorocyclohexane isomers may reduce the neurotoxic effects of lindane (ATSDR, 1992b).

MIXTOX has reported mixed results for studies of lindane and chlordane, lindane and hexachlorobenzene, lindane and toxaphene, and lindane and mirex interactions, including inhibition, no effect, and potentiation for these combinations in rodents exposed via gavage (MIXTOX, 1992).

5.3.9.10 Critical Data Gaps—

As discussed above, effects on both the male and female reproductive systems have been evaluated in short-term studies. Evaluation of these effects in a longer-term study, and identification of the underlying mechanisms of toxicity would provide information needed for a more complete evaluation of toxicity and dose-response dynamics. Additional information is also needed, as noted in Section 5.3.9.5, on the potential for exposure via lactation and on mechanisms and dose-response for premature labor and spontaneous abortion.

ATSDR has identified data gaps that include chronic duration oral studies; in vivo genotoxicity tests; reproductive, developmental immunotoxicity, and neurotoxicity studies; human studies correlating exposure levels with body burdens of lindane and with specific effects; and pharmacokinetic studies. A large group of international studies recently submitted to ATSDR are currently under review and six studies are ongoing in the United States (ATSDR, 1992b).

5.3.9.11 Summary of EPA Levels of Concern—

Chronic Toxicity	3×10^{-4} mg/kg/d
Carcinogenicity	1.3 per mg/kg/d.

5.3.9.12 Major Sources—

ATSDR (1992b), HSDB (1993), IRIS (1993).

5.3.10 Mirex

5.3.10.1 Background—

Mirex is a polymerizing agent and was used as an organochlorine pesticide and fire retardant until 1975 (U.S. EPA, 1993a). Mirex has the potential to concentrate many thousand-fold in food chains (Hayes and Laws, 1991).

5.3.10.2 Pharmacokinetics—

Mirex is a lipophilic compound and is readily taken up in fat tissue. The highest residues were found in fat and the liver. Based on a study in cows, it is also found in milk. At 0.01 and 1 ppm dietary exposure for 32 weeks, cows' milk levels were 0.01 to 0.08 ppm (U.S. EPA, 1993o).

No clear data on half-life in humans was found; however, studies in primates found that 90 percent of the original dose was retained in fat after 106 days. The researchers predicted that mirex had an extremely long half-life in monkeys. Based on this, mirex would be expected to have a very long half-life in humans.

5.3.10.3 Acute Toxicity—

See the listing of usual effects associated with organochlorine exposure in Appendix C. Acute hepatic effects have been observed in experimental animals. These may result from the following cytological effects: disaggregated ribosomes, glycogen depletion, formation of liposomes, and proliferation of smooth endoplasmic reticulum (U.S. EPA, 1993o).

5.3.10.4 Chronic Toxicity—

IRIS lists a chronic exposure RfD of 2×10^{-4} mg/kg/d for mirex based on a NOAEL of 0.07 mg/kg/d from a chronic dietary rat study. The IRIS file notes that the previous RfD was 2×10^{-6} mg/kg/d. The IRIS file states that a dose-related increase in hyperplasia of the parathyroid gland was observed in males in the critical study at and above 0.007 mg/kg/d (IRIS, 1993). It is not stated in the file why this value was not used as a LOAEL; although it is noted that the effect was not observed in other studies. Additional effects noted in the study were: nephropathy, renal medullary hyperplasia, multiple types of liver damage, splenic fibrosis, and cystic follicles of the thyroid. The RfD is based on the latter two effects. Uncertainty factors of 10 each were applied for inter- and intraspecies variability and a factor of 3 was applied for lack of a complete database (multigenerational data on reproductive effects and cardiovascular toxicity data). The IRIS file also indicates that effects on the testis (testicular degeneration, hypocellularity, and depressed spermatogenesis), which were noted in other studies, may not have been detected in the critical study because of age-related degenerative changes in the study animals (IRIS, 1993).

A subchronic study in rats identified an LEL of 0.01 mg/kg/d with liver lesions and thyroid injury at the lowest dose tested. Another subchronic study in rats noted similar effects with a NOEL of 0.01 in which only females were tested. A 21-month rat feeding study identified an LEL of 0.01 mg/kg/d based on histological lesions in the liver and thyroid and altered enzyme levels (U.S. EPA, 1993o). These results are supported by 28-day feeding studies, which identified LELs at a similar level to the studies listed above. Histopathology of the liver was noted at 0.025 mg/kg/d in two rat studies. No NOELs were identified (U.S. EPA, 1993o). Both structural and functional adverse effects on the thyroid have been observed in experimental animals. The effects persisted for more than 1 year after treatment ceased. Neurobehavioral effects have also been associated with mirex exposure (Hayes and Laws, 1991).

Both the longer-term and the subchronic studies, which identified LELs of 0.01 mg/kg/d, suggest that toxicity occurs at levels below those identified in the NTP study, which is used as the basis for the IRIS RfD. The lower LELs can be used to calculate an alternative estimated exposure limit. The standard uncertainty factors used in this calculation would typically take into consideration inter- and intraspecies variability and the use of an LEL rather than a NOAEL.

5.3.10.5 Developmental Toxicity—

Numerous developmental toxicity studies have been conducted on mirex. Effects associated with exposure include undescended testes (U.S. EPA, 1993o), fetal cataracts, edema, ectopic gonads, hydrocephaly, abnormal kidney enzyme levels, decreased brain and liver weights, scoliosis, runts, cleft palates, heart defects (anatomical), effects on the fetal electrocardiogram, and decreased fertility. Multiple studies have noted increased mortality and cataracts resulting from both pre- and postnatal exposure (IRIS, 1993). Many of the deaths have been due to congestive heart failure. Studies utilizing cross-fostering of litters have found that both cataracts and reduced viability were less pronounced when neonates did not receive their mothers' milk (mothers were dosed with mirex during pregnancy) (Hayes and Laws, 1991).

Mirex is lipophilic and has been found in human breast milk. A small study in the Great Lakes region found levels from 0.1 to 0.6 ppm in human milk (Hayes and Laws, 1991).

Many of the developmental studies noted significant effects at the lowest dose tested (e.g., cardiac function abnormalities occurred at the LOEL of 0.25 mg/kg/d) (IRIS, 1993). Consequently, they do not provide a useful threshold for effects. One study of cardiac effects in the fetus found a dose-related increase in first-degree heart block; however, the levels tested were quite high (5, 6, 7, and 10 mg/kg). A high rate of stillbirth and postnatal mortality, first- and second-degree heart blocks, respiratory distress, and cataracts was observed in a prenatal exposure study with an LEL of 1 mg/kg/d (U.S. EPA, 1993o).

A single dose of 1.25 mg/kg to pregnant rats caused reduced viability and growth and a high incidence of cataracts in offspring. A developmental study in rats identified an LEL of 0.25 mg/kg/d with an increase in stillborn pups and decreased viability. A one-generation mouse study identified an LEL of 0.075 mg/kg in a single dose causing reduced litter size; no NOEL was identified. A one-generation rat study identified an LEL of 0.125 mg/kg/d with decreased litter size, histopathological changes in the liver and thyroid, and cataracts (U.S. EPA, 1993o). Biochemical alterations include significant decreases in plasma protein concentrations and colloid osmotic pressure in fetuses (U.S. EPA, 1993o).

Mirex causes serious adverse effects in multiple organ systems in developing animals. Frank teratogenic effects are observed at levels that are much higher than those required to produce other effects. Teratogenic effects have been observed at an LEL of 6.0 mg/kg with an increased incidence of visceral anomalies and deciduomas. A teratogenic NOEL of 3.0 mg/kg was identified (U.S. EPA, 1993o).

Due to the absence of a NOEL for many of the effects, there is considerable uncertainty regarding the calculation of an exposure limit for developmental effects. However, the seriousness of the effects argues for inclusion of a developmental risk value to provide some guidance for exposure. Based on the

information reviewed, the most sensitive species appears to be the mouse, with effects observed at 0.075 mg/kg in a single dose (LEL). Studies in other species identified multiple effects at exposure levels equal to, or less than, a factor of twofold greater (0.125 and 0.25 mg/kg/d). If the mouse study results are used to calculate an estimated exposure limit for developmental effects, the standard uncertainty factors would typically take into consideration inter- and intraspecies variability and the use of an LEL rather than a NOAEL. Due to the multiple and serious effects associated with mirex exposure during development, and the potential for bioaccumulation and exposure through the placenta and via breast milk, an additional modifying factor may be applied.

As noted above, mirex accumulates in body tissue; consequently, exposure occurring prior to pregnancy can contribute to the overall maternal body burden and result in exposure to the developing individual. As a result, it is necessary to reduce exposure to children and women with childbearing potential to reduce overall body burden. If a female has been exposed to mirex, even if exposure is reduced during pregnancy, the outcome of that pregnancy may be affected, depending on the timing and extent of prior exposure.

5.3.10.6 Mutagenicity—

Most genotoxicity tests reported in the tox one-liners are bacterial assays and are negative (U.S. EPA, 1993o). A dominant lethal mutagenicity test in rats (in vivo) found a decreased incidence of pregnancy at 6 mg/kg/d with a NOEL of 3 mg/kg/d. Exposure took place over 10 days prior to mating. Additional information is needed on the nature of the toxicity.

5.3.10.7 Carcinogenicity—

Mirex has been classified as a probable human carcinogen (B2) based on liver and adrenal tumors in experimental animals. The cancer potency is 1.8 per mg/kg/d (HEAST, 1995). This chemical is currently under review by EPA.

5.3.10.8 Special Susceptibilities—

Juveniles may be more susceptible than adults based on the results of animal studies. At 60 ppm (approximately 3 mg/kg/d), adult mice exposed for 15 days experienced only weight loss; this level was lethal for young mice (Hayes and Laws, 1991).

Based on a review of the toxicity data above, individuals with diseases or disorders of the following organ systems may be at higher risk than the general population: kidney, liver, spleen, thyroid, parathyroid, cardiovascular, and male reproductive. Due to the developmental toxicity observed in experimental animals, prenatal exposure and lactation exposure may pose a risk to children.

See also a discussion of susceptibilities associated with pharmaceutical use in Appendix C.

5.3.10.9 Interactive Effects—

See a discussion of organochlorine effects related to induction of the mixed function oxidase system in Appendix C. No additional data were located.

MIXTOX reports mixed results for interactions between lindane and mirex and for Aroclor 1254 and mirex. Other studies of Aroclor and mirex have not found interactive results (MIXTOX, 1992).

5.3.10.10 Critical Data Gaps—

Additional information is needed on the developmental effects of mirex to identify a NOEL for sensitive developmental toxicity endpoints so that a well-founded exposure limit for developmental effects can be determined. In a related area, the mutagenicity data indicate a potential mutagenic effect based on in vivo studies. A better understanding of the relationship between the results of these types of studies and mutagenic effects in the human population is needed. The chronic exposure toxicity studies do not provide consistent results. Additional clarification of the NOELs for sensitive endpoints in this area is needed.

5.3.10.11 Summary of EPA Levels of Concern—

Chronic Toxicity	2×10^{-4} mg/kg/d
Carcinogenicity	1.8 per mg/kg/d.

5.3.10.12 Major Sources—

Hayes and Laws (1991), IRIS (1993), U.S. EPA (1993o).

5.3.11 Toxaphene

5.3.11.1 Background—

Toxaphene is an organochlorine pesticide that is comprised of a mixture of 670 chlorinated camphenes. It was banned for most uses in 1982; however, due to its relatively long half-life, it persists in the environment. The soil half-life is approximately 1 to 14 years (HSDB, 1993).

5.3.11.2 Pharmacokinetics—

Toxaphene is rapidly degraded via dechlorination, dehydrodechlorination, and oxidation, primarily through the action of the mixed function oxidase system and other hepatic microsomal enzymes. Conjugation may occur but is not a major route of metabolism. Each component of toxaphene has its own rate of biotransformation, making the characterization of toxaphene pharmacokinetics complex (ATSDR, 1990b).

Some adverse effects of toxaphene may result from repeated exposure that do not occur with a single exposure to a lesser dose. Exposures at 0.06 mg/kg/d over 5 weeks caused adrenal hormone reductions whereas a single dose of 16 mg/kg did not cause effects. This is significant when considering potential risks arising from chronic exposure to toxaphene (ATSDR, 1990b).

5.3.11.3 Acute Toxicity—

Acute high-level exposures to toxaphene have resulted in death in adults and children with an estimated minimum lethal dose of 2 to 7 g, which is equivalent to 29 to 100 mg/kg for an adult male. Long-term damage to the central nervous system and liver has also been observed. The kidney and adrenal glands are also target organs (ATSDR, 1990b). A 1-day NOAEL of 10 mg/kg/d is available from a dog study that used death as the effect of concern. A 14-day LOAEL of 5 mg/kg/d was identified in an 8-day study that was used as the basis for an MRL for acute exposure of 0.005 mg/kg/d by ATSDR (ATSDR, 1990b). See the listing of usual effects associated with organochlorine exposure in Appendix C.

5.3.11.4 Chronic Toxicity—

IRIS does not provide a discussion of chronic effects of exposure to toxaphene or an RfD (IRIS, 1993). The EPA Office of Water and Office of Pesticide Programs have calculated an RfD of 3.6×10^{-4} mg/kg/d based on the absence of liver, kidney, and thyroid effects in rats exposed to toxaphene via the oral route for 26 weeks.

Chronic exposure to toxaphene may result in damage to the following systems: liver, kidney, adrenal, immunological, and neurological. The use of the liver as the endpoint of concern is supported by a recent subchronic oral rat study that found NOAELs of 0.28 for males and 0.38 for females with liver and kidney effects (ATSDR, 1990b).

Chronic exposure to toxaphene may cause hormonal alterations. A study found increased levels of hepatic metabolism in vivo and in vitro of estradiol and estrone and a decrease in their uterotropic action. Duration of exposure was not specified in the source reviewed (HSDB, 1993). See also notes regarding estrogenic activity in Section 5.3.11.7.

5.3.11.5 Developmental Toxicity—

Adverse developmental effects, including immunosuppressive and behavioral effects, were noted in experimental animals at levels below those required to induce maternal toxicity. Immunosuppression (reduction in macrophage levels, cell-mediated immunity, and humoral immunity) was observed in test animals exposed during gestation and nursing with a LOAEL of 1.5 mg/kg/d. Impairment of behavioral maturation (e.g., reflexes) occurred at 0.05 mg/kg/d in a rat study with 47 days of exposure. Delayed ossification (bone development) and alterations in kidney and liver enzymes suggestive of organ-specific toxicity were observed

at 15 mg/kg/d. Other adverse effects noted in offspring of maternally exposed individuals included histological changes in the liver, thyroid, and kidney (ATSDR, 1990b).

Women exposed to toxaphene by entering a field that had recently been sprayed exhibited a higher incidence of chromosomal aberrations in cultured lymphocytes than was found in unexposed women. Dermal and inhalation were the probable routes of exposure; however, the exposure was not quantified (ATSDR, 1990b). Animal study results suggest that toxaphene does not interfere with fertility in experimental animals at the doses tested (up to 25 mg/kg/d) (ATSDR, 1990b). However, chromosomal aberrations (as observed in women) would lead to decreased fertility due to early fetal loss and may result in heritable birth defects.

Toxaphene is known to be conveyed into milk rapidly after maternal exposure to the chemical. The half-life of toxaphene has been estimated at 9 days. It has been found in the milk of cows at all doses tested (20 to 40 ppm). In cows exposed to 20 to 140 ppm in food (mg/kg/d conversion not available) for 8 weeks, milk concentrations increased rapidly; they decreased rapidly following cessation of exposure. Information was provided on the relationship between feed and milk concentrations. The exposure range was from 20 ppm feed with milk concentrations reaching 0.36 ppm to 140 ppm feed with a maximum of 1.89 ppm in milk (ATSDR, 1990b). It may be advisable to use these data to estimate the human dose to nursing infants.

Other aspects of developmental toxicity associated with toxaphene are based on effects observed in adult individuals that are known to pose higher risks to children. The ATSDR has cautioned that:

> embryos, fetuses, and neonates up to age 2 to 3 months may be at increased risk of adverse effects . . . because their enzyme detoxification systems are immature

and

> Infants and children are especially susceptible to immunosuppression because their immune systems do not reach maturity until 10 to 12 years of age (ATSDR, 1990b).

Immunosuppression was noted in multiple subchronic exposure animal studies.

ATSDR also noted that:

> animal studies suggest that detoxification of the toxaphene mixture may be less efficient in the immature human than the metabolism and detoxification of the single components such as Toxicant A or B (ATSDR, 1990b).

ATSDR provides an MRL for intermediate exposures (14 to 365 days) of 5×10^{-5} mg/kg/d based on an LEL of 0.05 mg/kg/d associated with impaired behavioral development. Uncertainty factors of 10 each for inter- and intraspecies variability and the use of an LEL were applied (ATSDR, 1990b). This value can be used as the estimated exposure limit for developmental effects in developing fish consumption limits.

As noted above, toxaphene accumulates in body tissue; consequently, exposure occurring prior to pregnancy can contribute to the overall maternal body burden and result in exposure to the developing individual. As a result, it is necessary to reduce exposure to children and women with childbearing potential to reduce overall body burden. If a female has been exposed to toxaphene, even if exposure is reduced during pregnancy, the outcome of that pregnancy may be affected, depending on the timing and extent of prior exposure.

5.3.11.6 Mutagenicity—

There are numerous positive mutagenicity assays of toxaphene: the Ames test, sister chromatid exchange, chromosomal aberrations in toxaphene-exposed humans, and forward mutation assays. The implications of this for human germ cells is not known and one assay designed to assess the effects of dominant lethal effects on implantations in mice yielded negative results. Some data suggest that the polar fraction of toxaphene may be more mutagenic than the nonpolar fraction (ATSDR, 1990b; HSDB, 1993).

Changes in human genetic material have been noted in workers exposed to toxaphene (HSDB, 1993).

5.3.11.7 Carcinogenicity—

Toxaphene is classified as a probable human carcinogen (B2) by EPA based on oral studies in animals. The cancer potency is 1.1 per mg/kg/d, based on liver tumors in experimental animals (IRIS, 1992). This value was used to calculate fish consumption limits listed in Section 4 for carcinogenic effects. No conclusive human epidemiological studies are available for toxaphene (ATSDR, 1990b).

Toxaphene has recently been observed to have estrogenic effects on human breast cancer estrogen-sensitive cells (Soto et al., 1994). Xenoestrogens have been hypothesized to have a role in human breast cancer (Davis et al., 1993). In addition to potential carcinogenic effects, toxaphene may also cause disruption of the endocrine system due to its estrogenic activity (Soto et al., 1994).

5.3.11.8 Special Susceptibilities—

A protein-deficient diet may increase the toxicity of toxaphene approximately threefold based on an LD_{50} study in rats (ATSDR, 1990b). Because this information was obtained from an LD_{50} study, it cannot be used directly to modify risk values. The Centers for Disease Control has specified that:

> This has important implications with regard to the possible increased susceptibility of humans who ingest a protein-deficient diet and live in areas of potential exposure to toxaphene. (ATSDR, 1990b)

If a population with protein-deficient diets is the target group for fish consumption limits, an additional modifying factor of 10 could be used in determining the appropriate exposure limit for developmental effects. A factor of 10 rather than 3 (observed in animal studies) is recommended because it is unknown whether human populations exposed under the same conditions will be more or less susceptible than the animals tested and because the results were obtained from an LD_{50} study rather than a study with a more sensitive toxic endpoint.

The nervous system is a primary target of toxaphene toxicity. Individuals with latent or clinical neurological diseases, such as epilepsy or behavioral disorders, may be at higher risk. In addition, children may be especially susceptible to toxaphene-induced neurotoxicity based on early reports of acute ingestion toxicity (ATSDR, 1990b).

As discussed in Section 5.3.11.5, ATSDR has identified pregnant women, fetuses, infants, and children as populations at greater risk. Other individuals who may be at higher risk are those with diseases of the renal, nervous, cardiac, adrenal, and respiratory systems. Individuals using certain medications are also at potential risk due to the induction of hepatic microsomal enzymes by toxaphene (discussed further in the following section).

See also a discussion of susceptibilities associated with pharmaceutical use in Appendix C.

5.3.11.9 Interactive Effects—

Metabolism of some drugs and alcohol may be affected by toxaphene's induction of hepatic microsomal enzymes. This was observed in a man using warfarin as an anticoagulant while he used toxaphene as an insecticide. The effectiveness of the drug was reduced due to its increased metabolism arising from toxaphene's induction of microsomal enzymes (ATSDR, 1990b).

See a discussion of organochlorine effects related to induction of the mixed function oxidase system in Appendix C.

Based on acute studies and anecdotal reports of acute exposure in humans, exposure to chemicals that increase microsomal mixed-function oxidase systems (e.g., lindane) are likely to reduce the acute toxicity of other chemicals detoxified by the same system (e.g., toxaphene) because the system is functioning at a higher than normal level. Toxaphene, in turn, reduces the acute toxicity of chemicals that require this system for detoxification (ATSDR, 1990b).

In experimental animals, toxaphene antagonized the tumorigenic activity of benzo(*a*)pyrene in the lung. It was theorized that this occurred because toxaphene inhibited the biotransformation of B(*a*)P to a reactive metabolite or by promoting its degradation to nonactive forms (ATSDR, 1990b).

MIXTOX has reported synergism between chlordane, toxaphene, and malathion in mice exposed via gavage and additive interactions between chlordane and toxaphene. Antagonism was reported between toxaphene and diazinon in rats exposed via gavage. Mixed results have been obtained between lindane and toxaphene (MIXTOX, 1992).

5.3.11.10 Critical Data Gaps—

The following data gaps have been identified by ATSDR, EPA, and NTP: mammalian germ cell genotoxicity, studies that investigate sensitive developmental toxicity endpoints including behavioral effects, epidemiological and animal studies of immunotoxicity, long-term neurotoxicity studies in animals using sensitive functional and neuropathological tests and behavioral effects on prenatally exposed animals, epidemiological studies evaluating multiple organ systems, and pharmacokinetic studies (ATSDR, 1990b).

5.3.11.11 Summary of EPA Levels of Concern—

Chronic Toxicity	3.6×10^{-4} mg/kg/d
Carcinogenicity	1.1 per mg/kg/d.

5.3.11.12 Major Sources—

ATSDR (1990b), HSDB (1993), IRIS (1993).

5.4 ORGANOPHOSPHATE PESTICIDES

In addition to the discussions of individual target analytes, please refer to the discussion of toxicity characteristics of the organophosphate chemical group in Appendix C.

5.4.1 Chlorpyrifos

5.4.1.1 Background—

Chlorpyrifos is an organophosphate insecticide that is applied throughout the United States for various agricultural uses.

5.4.1.2 Pharmacokinetics—

Chlorpyrifos accumulates in fat and has a longer half-life in fatty tissues than in other tissues. It has been detected in cows' milk (HSDB, 1993) and would be expected to occur in human milk of exposed mothers. This is of concern because organophosphates may have a higher toxicity for immature individuals than adults (e.g., malathion was more toxic to juveniles in three species tested) (U.S. EPA, 1992g). Chlorpyrifos is rapidly metabolized and excreted based on studies in animals (Hayes and Laws, 1991).

5.4.1.3 Acute Toxicity—

See the listing of usual effects associated with organophosphate exposure in Appendix C.

5.4.1.4 Chronic Toxicity—

IRIS provides an oral RfD of 0.003 mg/kg/d based on a NOAEL in a 20-day study reported in 1972 that found cholinesterase inhibition in adult male humans after 9 days of exposure. There were four subjects per dosed group. An uncertainty factor of 10 was used to calculate the RfD (IRIS, 1993). There are limitations in the use of this study for a chronic toxicity RfD. Although effects were observed at levels lower than the NOAEL, they were discounted due to an inability to achieve statistical significance; however, it is very difficult to achieve statistical significance with four subjects. No uncertainty factor was applied for the acute nature of the study. Most important, EPA is reviewing its methods for evaluating cholinesterase inhibitors. Cholinesterase inhibition alone is not necessarily considered an adverse effect in the absence of other effects. Problems related to the use of cholinesterase inhibition as a critical endpoint are discussed in Appendix C. The value listed on IRIS was confirmed in 1993 by an Office of Pesticide Programs RfD Peer-Review Committee (U.S. EPA, 1993e).

Other chronic exposure effects have been observed in study animals. In a 1991 two-generation rat study, adrenal lesions were reported at 1 and 5 mg/kg/d. In a

subchronic study at higher doses, the same effects were observed along with increased brain and heart weight (U.S. EPA, 1992g).

There are significant uncertainties regarding an appropriate threshold for effects of chlorpyrifos exposure. These include the very limited data on the recently identified adrenal and cardiac effects of chlorpyrifos and the utility of a cholinesterase endpoint. The IRIS value was used to calculate fish consumption limits shown in Section 4 for chronic toxicity. Future improvements in the database may result in alteration in this recommended value.

5.4.1.5 Developmental Toxicity—

Chlorpyrifos is fetotoxic in numerous species. In a 1987 rat study, a developmental toxicity NOEL of 2.5 mg/kg/d was determined; at the LOEL of 15 mg/kg/d postimplantation losses were observed. In a 1991 rat study, which was rated as "guideline" by OPP, a developmental NOEL of 1 mg/kg/d was obtained, with increased pup mortality at 5 mg/kg/d. No data were available for this document on underlying causes of mortality. Decreased fetal length and increased skeletal variants were noted in mice with a fetotoxic NOEL for the study of 10 mg/kg/d. In a 1987 study on rabbits, increased skeletal variants and an increased incidence of unossified sternebra and xiphisternum were observed at 81 mg/kg/d (U.S. EPA, 1992g).

A 1991 rat study yielded the most conservative NOEL at 1 mg/kg/d. Unfortunately, the observed endpoint was mortality. An evaluation of the underlying causes of mortality may yield a more sensitive endpoint. If this study were used to estimate an exposure limit for developmental effects, the standard uncertainty factors used in this calculation would typically take into consideration inter- and intraspecies variability and data gaps, based on the inability of the current studies to identify critical information.

Currently available data regarding developmental toxicity are limited because endpoints identified were gross measures of toxicity (death) and the underlying causes of toxicity were not identified. The studies are not based on sensitive measures of developmental toxicity. In cases such as this, where the available studies provide information only on gross measures of toxicity (i.e., death), it may be advisable to use the RfD for chronic toxicity and consider modifications for application to pregnant women and children.

5.4.1.6 Mutagenicity—

The results of mutagenicity assays of chlorpyrifos are mixed. Chlorpyrifos was weakly positive with and without activation in gene conversion and recombination assays and positive for direct damage to DNA in *B. subtilis* (U.S. EPA, 1992g). In vivo assays of mouse liver DNA and RNA indicated that chlorpyrifos caused more DNA and RNA alkylation than other organophosphates (HSDB, 1993). Its toxicity is probably related to formation of its oxon analog (chlorpyrifosoxon) and

subsequent enzyme inhibition of cholinesterase activity, carboxylases, and mitochondrial oxidative phosphorylases.

5.4.1.7 Carcinogenicity—

Insufficient information is available to determine the carcinogenic status of chlorpyrifos.

5.4.1.8 Special Susceptibilities—

See a discussion of susceptibilities associated with organophosphate exposure in Appendix C.

5.4.1.9 Interactive Effects—

No data were located.

5.4.1.10 Critical Data Gaps—

IRIS lists the following data gap: chronic feeding/oncogenicity study in rats (IRIS, 1993). Additional data are needed on the noncholinesterase effects of chronic exposure and on the toxicity that underlies early pup mortality in developmental studies.

5.4.1.11 Summary of EPA Levels of Concern—

Chronic Toxicity	3×10^{-3} mg/kg/d
Carcinogenicity	Insufficient data to determine carcinogenic status.

5.4.1.12 Major Sources—

HSDB (1993), IRIS (1993), U.S. EPA (1992g).

5.4.2 Diazinon

5.4.2.1 Background—

Diazinon is an organophosphorus insecticide that has been widely used since its introduction in 1952.

5.4.2.2 Pharmacokinetics—

Very little data were located. Metabolism appears to proceed by similar but somewhat different paths in various mammalian species (HSDB, 1993). Human milk may contain trace amounts of diazinon based on the results of exposure in cows (HSDB, 1993).

5.4.2.3 Acute Toxicity—

Diazinon is highly toxic. The estimated adult oral fatal dose is approximately 25 g (HSDB, 1993). See the listing of usual effects associated with organophosphate exposure in Appendix C.

5.4.2.4 Chronic Toxicity—

IRIS does not currently provide an oral RfD because it is under review within the Agency (IRIS, 1993). OPP provides an RfD of 9×10^{-5} mg/kg/d based upon cholinesterase inhibition observed in a 90-day rat feeding study with a NOEL of 0.009 mg/kg/d and uncertainty factors totaling 100 (U.S. EPA, 1992d). Problems related to the use of cholinesterase inhibition as a critical endpoint are discussed in Appendix C.

Very little dose-response data are available on chronic systemic toxicity, other than cholinesterase effects. Hematocrit depression was observed in a rat chronic feeding study at 50 mg/kg/d. Gastrointestinal disturbances were noted at 5 mg/kg/d with a NOEL of 0.05 mg/kg/d in a chronic monkey study (U.S. EPA, 1993f). If an alternative to cholinesterase inhibition is required, the monkey study can be used with standard uncertainty factors that take into consideration inter- and intraspecies variability.

5.4.2.5 Developmental Toxicity—

The reproductive/teratogenic studies listed in the tox one-liners report no adverse effects at the highest doses tested (U.S. EPA, 1993f).

HSDB reported multiple studies indicating diazinon is teratogenic. In a prenatal exposure study (dose not specified), multiple doses of diazinon resulted in a higher incidence of urinary malformations, hydronephrosis, and hydroureter. Diazinon was teratogenic in rats administered a single dose on day 11 of gestation. Decreased fetal body weight was the most sensitive indicator. No dose was specified in the database (HSDB, 1993). In chicks, diazinon exposure led to abnormal vertebral column development including a tortuous and shortened structure with abnormal vertebral bodies. In the neck region, the vertebral bodies had fused neural arches and lacked most intervertebral joints. More severe effects on other elements of the skeleton were observed at higher doses (HSDB, 1993; Hayes, 1982). The dose (1 mg/egg) is not easily convertible to a mammalian dose.

Behavioral effects were observed in mice exposed prenatally at 0.18 and 9 mg/kg/d throughout gestation. The high-dose group showed decreased growth, several behavioral effects, and structural pathology of the forebrain. The low-dose group did not have brain pathology or growth abnormalities; however, they showed small but measurable defects in behavior and a delay in reaching maturity (Hayes, 1982). This study appears to provide a relatively sensitive endpoint for evaluation of developmental effects associated with exposure to diazinon. If the LOAEL of 0.18 mg/kg/d were used, the uncertainty factors would typically take into

consideration inter- and intraspecies variability and the use of a LOAEL rather than a NOAEL. Based on the available information, the current IRIS RfD would be protective against developmental toxicity.

5.4.2.6 Mutagenicity—

Most mutagenicity assays were negative; one positive sister chromatid exchange assay was noted (U.S. EPA, 1993f). A study on the effect of diazinon on mitosis in human lymphocytes reported chromosomal aberrations in 74 percent of the cells at 0.5 mg/mL (HSDB, 1993).

5.4.2.7 Carcinogenicity—

Insufficient information is available to determine the carcinogenic status of diazinon.

5.4.2.8 Special Susceptibilities—

See a discussion of susceptibilities associated with organophosphate exposure in Appendix C.

5.4.2.9 Interactive Effects—

MIXTOX has reported antagonistic effects between diazinon and toxaphene with exposure in rats via gavage (MIXTOX, 1992).

5.4.2.10 Critical Data Gaps—

OPP lists the following data gaps: reproduction study in rats, chronic feeding oncogenicity study in rats, and chronic feeding study in dogs (U.S. EPA, 1992d). A multigeneration reproductive study that evaluated developmental effects at low doses and defined a NOAEL would be useful in establishing an appropriate RfD.

5.4.2.11 Summary of EPA Levels of Concern—

Chronic Toxicity	9×10^{-5} mg/kg/d based on cholinesterase inhibition
Carcinogenicity	Insufficient information to determine carcinogenic status.

5.4.2.12 Major Sources—

Hayes (1982), HSDB (1993), U.S. EPA (1993f).

5.4.3 Disulfoton (disyston)

5.4.3.1 Background—

Disulfoton is an organophosphate pesticide with high acute toxicity to all mammals.

5.4.3.2 Pharmacokinetics—

Metabolism of disulfoton involves sequential oxidation of the thioether sulfur and/or oxidative desulfuration in addition to hydrolytic cleavage. The major metabolites are the sulfoxide acid sulfone analogs of the compound. These are toxic metabolites that are degraded rapidly to water-soluble nontoxic metabolites. Their estimated half-life is 30 to 32 hours (U.S. EPA, 1993h). Disulfoton is rapidly absorbed through the mucous membrane of the digestive system and conveyed by the blood to body tissues. The kidneys are the main route of elimination (HSDB, 1993).

5.4.3.3 Acute Toxicity—

See the listing of usual effects associated with organophosphate exposure in Appendix C. The acute oral LD_{50} in animals ranges from 2 to 27.5 mg/kg (U.S. EPA, 1993h). Disulfoton is highly toxic to all mammals by all routes of exposure (HSDB, 1993).

5.4.3.4 Chronic Toxicity—

IRIS provides an RfD of 4.0×10^{-5} mg/kg/d based on an LEL of 0.04 mg/kg/d from a 2-year rat study that was associated with cholinesterase inhibition and optic nerve degeneration (IRIS, 1993). The IRIS RfD was calculated using a modifying factor of 10 to account for possible findings in the additional recommended optic toxicity studies (U.S. EPA, 1992c). Standard methods would typically utilize 10 each for inter- and intraspecies variability and for the use of an LEL rather than a NOEL. This plus the modifying factor of 10 would yield an RfD of 4×10^{-6} mg/kg/d. Although there is some question regarding the use of cholinesterase inhibition as the basis for establishing an RfD (problems related to the use of cholinesterase inhibition as a critical endpoint are discussed in Appendix C), optic effects also serve as the basis for this RfD (U.S. EPA, 1992d).

Numerous other effects of disulfoton have been reported at doses within 1 order of magnitude of the LEL identified in the critical study. Significant toxicity in multiple organ systems has been observed at 0.1 mg/kg/d (the lowest dose tested) for the following systems: spleen, liver, pituitary, brain, seminal vesicles, and kidneys (IRIS, 1993). In addition, at 0.65 mg/kg/d, rats exhibited atrophy of the pancreas, chronic inflammation and hyperplasia in the stomach, and skeletal muscle atrophy (U.S. EPA, 1993h). Based on the chronic exposure information reviewed and standard assumptions regarding the use of uncertainty factors, the IRIS RfD appears to be protective against the effects listed above.

5.4.3.5 Developmental Toxicity—

In a rat teratogenicity study, incomplete ossification of the parietals and sternebrae were noted at 1 mg/kg/d with a NOEL of 0.3 mg/kg/d in rats. In a 1966 three-generation reproduction study in rats, male offspring had juvenile hypoplasia in the testes, females had mild nephropathy in the kidneys, and both had preliminary

stages of liver damage at 0.5 mg/kg/d. No NOEL was obtained, and no data were provided on a number of critical parameters, including weight, growth rate, and number of stillborn animals. Insufficient histologic data and incomplete necropsy reports were identified by EPA reviewers (IRIS, 1993, and U.S. EPA, 1993h). Toxicity was incompletely characterized in this study, and additional studies are needed to provide an adequately defined NOEL for developmental effects. Because multiple serious effects were observed at the lowest dose tested, the multigeneration study does not provide an optimal basis for calculation of an exposure limit for developmental effects. However, it does indicate that adverse developmental effects may occur with exposure to disulfoton and provides greater detail on these effects than do the other studies available.

A more recent two-generation rat study identified a NOEL of 0.04 mg/kg/d with an LEL of 0.12 mg/kg/d based on decreased litter sizes, pup survival, and pup weights at the LEL (U.S. EPA, 1993h). This study does not appear to provide the same level of analysis of sensitive endpoints as the three-generation study discussed above. However, it identifies a lower NOEL and LEL than the two older studies. If this study is used to calculate an estimated exposure limit for developmental effects, the uncertainty factors typically used in this calculation would take into consideration inter- and intraspecies variability. A modifying factor could be used for the lack of data on the level at which toxicity occurred that led to death. Additional studies are needed to identify the NOEL for sensitive measures of the testicular, liver, and kidney toxicity identified in the multigeneration study.

5.4.3.6 Mutagenicity—

Disulfoton was not mutagenic in most assays; however, it was positive for unscheduled DNA synthesis without activation in human fibroblasts, in a reverse mutation assay in salmonella (U.S. EPA, 1993h), and in other in vitro assays (HSDB, 1993).

5.4.3.7 Carcinogenicity—

Insufficient information is available to determine the carcinogenic status of disulfoton.

5.4.3.8 Special Susceptibilities—

Based on the organ toxicities observed in animal studies, individuals with diseases or disorders of the following systems may be at greater risk from exposure to disulfoton: pancreas, stomach, spleen, liver, pituitary, brain, seminal vesicles, kidneys, musculoskeletal, and ocular. In addition, children who were exposed prenatally to disulfoton may be at risk, depending on the level of exposure. Also see a discussion of susceptibilities associated with organophosphate exposure in Appendix C.

5.4.3.9 Interactive Effects—

No data were located.

5.4.3.10 Critical Data Gaps—

The IRIS file notes that additional rat reproduction studies and studies to evaluate the ocular effects of disulfoton are needed (IRIS, 1993). HSDB notes that, because of data gaps, a full risk assessment cannot be completed. Major relevant data gaps noted under the FIFRA heading in HSDB include chronic toxicity, oncogenicity, and mutagenicity data; animal metabolism; subchronic toxicity; and human dietary and nondietary exposures (some data gaps may have been filled, cited in HSDB, 1993). As noted above, additional studies are needed to identify the NOEL for sensitive measures of the testicular, liver, and kidney toxicity identified in the multigeneration study.

5.4.3.11 Summary of EPA Levels of Concern—

Chronic Toxicity	4×10^{-5} mg/kg/d
Carcinogenicity	Insufficient data to determine carcinogenic status.

5.4.3.12 Major Sources—

HSDB (1993), IRIS (1993), U.S. EPA (1993h).

5.4.4 Ethion

5.4.4.1 Background—

Ethion is an organophosphate pesticide used primarily on citrus crops (U.S. EPA, 1993a).

5.4.4.2 Pharmacokinetics—

No data were located.

5.4.4.3 Acute Toxicity—

See the listing of usual effects associated with organophosphate exposure in Appendix C.

5.4.4.4 Chronic Toxicity—

A 1970 study of 10 men (six test subjects) with a NOEL of 0.05 mg/kg/d found plasma and brain cholinesterase inhibition (IRIS, 1993). IRIS provides an RfD of 5×10^{-4} mg/kg/d based on a subchronic study in dogs that found a NOEL of 0.06 and 0.07 mg/kg/d for males and females, respectively, with the same effects as the

human study. Uncertainty factors of 10 each for intraspecies sensitivity and for the effects observed at 0.71 mg/kg/d in the dog study (IRIS, 1993). Problems related to the use of cholinesterase inhibition as a critical endpoint are discussed in Appendix C.

5.4.4.5 Developmental Toxicity—

A developmental NOEL of 0.6 mg/kg/d was obtained in a rat study that found delayed ossification at an LEL of 2.4 mg/kg/d (IRIS, 1993). A rabbit study by the same laboratory also identified an LEL of 2.4 mg/kg/d with an increased incidence of fused sternal centers and fetal resorptions at that dose level. The NOEL was 0.6 mg/kg/d (U.S. EPA, 1993n). A three-generation rat study was also listed in the tox one-liners; however, information was provided only on cholinesterase inhibition levels (U.S. EPA, 1993n).

The NOEL of 0.6 mg/kg/d from the rat and rabbit studies can be used to calculate an estimated exposure limit for developmental effects. The uncertainty factors would typically take into consideration inter- and intraspecies variability. Teratogenic effects and fetal death often occur at exposure levels considerably higher than levels associated with systemic toxicity. Other organophosphates have shown this gradient of effects (see diazinon, Section 5.4.2). Consequently, there is concern that the studies available for evaluation may not fully characterize the developmental toxicity of ethion.

In cases such as this, where the available studies provide information on only gross measures of toxicity (i.e., death), it may be advisable to use the RfD for chronic toxicity and consider modifications for application to pregnant women and children.

5.4.4.6 Mutagenicity—

The tox one-liners listed no positive study results.

5.4.4.7 Carcinogenicity—

Insufficient information is available to determine the carcinogenic status of ethion.

5.4.4.8 Special Susceptibilities—

See a discussion of susceptibilities associated with organophosphate exposure in Appendix C.

5.4.4.9 Interactive Effects—

Potentiation between ethion and malathion has been observed. In rats, the potentiation was approximately 2.9-fold. In dogs, there was very slight, if any, potentiation (U.S. EPA, 1993n).

5.4.4.10 Critical Data Gaps—

IRIS lists a chronic dog feeding study as a data gap (IRIS, 1993). A multigeneration study and a developmental study that evaluate neurobehavioral toxicity are needed to clarify developmental effects.

5.4.4.11 Summary of EPA Risk Values—

Chronic Toxicity	5×10^{-4} mg/kg/d
Carcinogenicity	Insufficient data to determine carcinogenic status.

5.4.4.12 Major Sources—

IRIS (1993), U.S. EPA (1993n).

5.4.5 Terbufos

5.4.5.1 Background—

Terbufos is an organophosphorus insecticide.

5.4.5.2 Pharmacokinetics—

No data were located.

5.4.5.3 Acute Toxicity—

Terbufos has a high acute toxicity to humans. Animal studies yielded the following results: an oral LD_{50} in rats of 1.3 to 1.6 mg/kg (surveillance index) and an oral LD_{50} in mice of 1.3 to 6.6 mg/kg (U.S. EPA 1992f). See the listing of usual effects associated with organophosphate exposure in Appendix C.

5.4.5.4 Chronic Toxicity—

Limited information is available on terbufos toxicity and the focus of most toxicity evaluations is on its cholinesterase inhibition properties. IRIS does not provide an RfD for terbufos. HEAST lists an RfD of 2.5×10^{-5} mg/kg/d based on cholinesterase inhibition in a 6-month dietary dog study with a NOEL of 0.0025 mg/kg/d. Uncertainty factors of 10 each for inter- and intraspecies variation were used. No uncertainty factor was used for the subchronic nature of the study. The HEAST table states that this value is under review (HEAST, 1992). OPP has calculated an RfD of 1.3×10^{-4} mg/kg/d for terbufos (U.S. EPA, 1996b).

Quantitative chronic toxicity information on cholinesterase inhibition is available. In rats, a 1974 lifetime oral study found a LOEL of 0.0125 mg/kg/d (the lowest dose tested); a 1987 1-year oral study found a NOEL of 0.025 mg/kg/d. In dogs, a 1972 6-month oral study found a NOEL of 0.0025 mg/kg; a 1986 1-year study

found a LOEL of 0.015 mg/kg/d (the lowest dose tested); a 1987 28-day dog study identified a NOEL of 0.00125 mg/kg/d (U.S. EPA, 1992f).

Quantitative data on chronic effects that are not directly related to cholinesterase inhibition are limited, due to the lack of "no effect levels" from many studies and the need for specific information on some effects. Chronic exposure effects include: corneal cloudiness and opacity, eye rupture, alopecia, disturbances in balance, and exophthalmia noted in multiple studies and multiple species at 0.0125 mg/kg/d and above (U.S. EPA, 1992f). Increased liver weight and increased liver extramedullary hematopoiesis at 0.025 mg/kg/d and above, and mesenteric and mandibular lymph node hyperplasia at 0.05 mg/kg/d and above were noted in a subchronic (3-month) rat study (animals were not examined for this lesion at lower exposure levels) (U.S. EPA, 1992f).

5.4.5.5 Developmental Toxicity—

Data currently available on developmental toxicity are limited because the endpoints identified were gross measures of toxicity (death) and the underlying causes of toxicity were not identified. The studies are not based on sensitive measures of developmental toxicity. Results from two developmental studies and one multigeneration study are available: a 1984 rat study found a NOEL of 0.1 mg/kg/d with increased fetal resorptions at 0.2 mg/kg/d; a 1988 rabbit study identified a NOEL of 0.25 mg/kg/d with fetal resorptions at 0.5 mg/kg/d. A 1973 multigeneration reproductive study found a NOEL of 0.0125 mg/kg/d in rats, based on an increase in the percentage of deaths in offspring (U.S. EPA, 1992f).

The increase in deaths in offspring in the multigeneration study does not provide insight into the causes of death. Fetal resorptions, noted in the developmental studies, often result from gross abnormalities leading to early fetal death or from direct fetotoxicity. A NOEL for adverse effects would be a preferable endpoint, with exploration of the causes underlying fetal loss. A multigeneration study that evaluated sensitive endpoints, including ocular effects and liver and lymph node toxicity, which were observed at low doses in adults animals (see Section 5.4.5.4), would provide a better basis for determining a safe developmental exposure level.

Based on the developmental data currently available, the multigeneration study NOEL of 0.0125 appears to be the most sensitive study (perhaps because exposure occurred over a longer period of time than in the other developmental toxicity studies). However, the developmental toxicity database embodies considerable uncertainty. Many chronic exposure effects were observed at levels approximating the NOEL obtained from the multigeneration study. Although these effects were not reported in the developmental toxicity studies, it is not known whether effects observed in adult studies, such as liver and lymph node toxicity, were evaluated in the developmental studies. Postnatal exposure would be expected to be at least as toxic to young individuals as to adults.

If the multigeneration study is used to calculate an exposure limit for developmental effects, the standard uncertainty factors would typically take into

consideration intra- and interspecies variability and the inadequacy of the database. In cases such as this, where the available studies provide information on only gross measures of toxicity (i.e., death), it may be advisable to use the RfD for chronic toxicity and consider modifications for application to pregnant women and children.

5.4.5.6 Mutagenicity—

Terbufos was negative in most assays. It was positive in an in vivo dominant-lethal assay in rats; at 0.4 mg/kg, the numbers of viable implants was reduced (U.S. EPA, 1992f).

5.4.5.7 Carcinogenicity—

Insufficient information is available to determine the carcinogenic status of terbufos.

All oncogenicity tests on terbufos have been considered negative by OPP (U.S. EPA, 1992f). However, further exploration of mesenteric and mandibular lymph node hyperplasia identified in a 3-month study (noted above) is warranted because hyperplasia is often a precancerous condition. Evaluation of this endpoint in a lifetime study is necessary to determine the ultimate course of the hyperplasia.

5.4.5.8 Special Susceptibilities—

See a discussion of susceptibilities associated with organophosphate exposure in Appendix C.

5.4.5.9 Interactive Effects—

No data were located.

5.4.5.10 Critical Data Gaps—

There are inconsistencies in the toxicity database for terbufos based on a comparison of acute study results and the results obtained in some chronic feeding studies, developmental studies, and the LD_{50}s. Some longer-term studies reported no effects at exposure levels above the LD_{50}s (U.S. EPA, 1992f).

The animal and human studies available on terbufos do not provide a complete and consistent basis for calculation of an alternative exposure limit. The identification of mesenteric and mandibular lymph node hyperplasia is problematic due to its potential oncogenic implications. A NOEL for these effects was not identified and effects were not screened in low dose groups. Other effects, which are not directly related to cholinesterase inhibition, were also noted with terbufos exposure, including optic damage at 0.0125 mg/kg/d in multiple species and studies. In addition, there is uncertainty regarding a safe exposure level to prevent adverse developmental effects, as discussed above. These results warrant further

evaluation and may be considered, by some, to justify an additional modifying factor to deal with data gaps and uncertainties in the database.

5.4.5.11 Summary of EPA Levels of Concern—

Chronic Toxicity	1.3×10^{-4} mg/kg/d
Carcinogenicity	Insufficient data to determine carcinogenic status.

5.4.5.12 Major Sources—

HSDB (1993), U.S. EPA (1992f).

5.5 CHLOROPHENOXY HERBICIDES

5.5.1 Oxyfluorfen

5.5.1.1 Background—

Oxyfluorfen is a recently introduced diphenyl ether pesticide in the chlorophenoxy class. Limited data were located on this chemical.

5.5.1.2 Pharmacokinetics—

No data were located.

5.5.1.3 Acute Toxicity—

The acute oral LD_{50} in rats is greater than 5,000 mg/kg (Hayes and Laws, 1991).

5.5.1.4 Chronic Toxicity—

IRIS provides an RfD of 3×10^{-3} mg/kg/d based on a NOAEL of 0.3 mg/kg/d from a 1977 20-month mouse feeding study that identified nonneoplastic lesions in the liver and increased absolute liver weight. Uncertainty factors of 10 each for inter- and intraspecies sensitivity were applied (IRIS, 1993).

5.5.1.5 Developmental Toxicity—

A three-generation rat study provided a NOEL of 0.5 mg/kg/d and an LEL of 5 mg/kg/d. A rat teratology study identified a fetotoxic NOEL of 100 mg/kg/d. A rabbit study found fused sternebrae at 30 mg/kg/d and a NOEL of 10 mg/kg/d (IRIS, 1993, U.S. EPA, 1993l). A rabbit teratology study data gap is noted in the IRIS file (IRIS, 1993). Nitrofen, a close structural relative of oxyfluorfen has been studied more extensively. Studies of nitrofen identified multiple varied developmental abnormalities associated with prenatal exposure (Hayes and Laws, 1991).

The multigeneration study is the most sensitive study of those reviewed; this may be due to the longer period of exposure and followup than the prenatal exposure studies. The standard uncertainty factors used in this calculation would typically take into consideration inter- and intraspecies variability. Additional information is needed on the nature of effects at the LEL.

5.5.1.6 Mutagenicity—

Results of mutagenicity assays on oxyfluorfen are mixed (U.S. EPA, 1993l).

5.5.1.7 Carcinogenicity—

Oxyfluorfen has been classified as a possible human carcinogen (C) based on liver tumors identified in experimental animals. A cancer potency of 0.13 is provided by OPP (U.S. EPA, 1992d).

5.5.1.8 Interactive Effects—

No data were located.

5.5.1.9 Critical Data Gaps—

The IRIS file notes a rabbit teratology study as a data gap.

5.5.1.10 Summary of EPA Levels of Concern—

Chronic Toxicity	3×10^{-3} mg/kg/d
Carcinogenicity	0.13 per mg/kg/d.

5.5.1.11 Major Sources—

IRIS (1993), U.S. EPA (1993l).

5.6 POLYCYCLIC AROMATIC HYDROCARBONS (PAHs)

5.6.1 Background

Polycyclic aromatic hydrocarbons (PAHs) are a group of organic chemicals that have a fused ring structure of two or more benzene rings. PAHs are also commonly referred to as polynuclear aromatic hydrocarbons (PNAs). They are formed during the incomplete combustion of organic materials. Industrial activities that produce PAHs include coal coking; production of carbon blacks, creosote, and coal tar; petroleum refining; synfuel production from coal; and the use of Soderberg electrodes in aluminum smelters and ferrosilicum and iron works (U.S. EPA, 1995). Domestic activities that produce PAHs include cigarette smoking, home heating with wood or fossil fuels, waste incineration, broiling and smoking foods, and use of internal combustion engines. PAHs are ubiquitous in the environment and usually occur as mixtures. PAHs with two to five benzene rings are generally of greatest concern for environmental and human health effects (U.S. EPA, 1995). ATSDR (1995) has identified the following PAHs as the most important with regard to human exposure:

- Acenaphthene
- Acenaphthylene
- Anthracene
- Benz[*a*]anthracene
- Benzo[*a*]pyrene
- Benzo[*e*]pyrene
- Benzo[*b*]fluoranthene
- Benzo[*k*]fluoranthene
- Benzo[*j*]fluoranthene
- Benzo[*g,h,i*]perylene
- Chrysene
- Dibenz[*a,h*]anthracene
- Fluoranthene
- Fluorene
- Indeno[*1,2,3-cd*]pyrene
- Phenanthrene
- Pyrene.

Although these and many other PAHs are present in the environment, benzo[*a*]pyrene is the chemical with most of the available health effects data.

5.6.2 Pharmacokinetics

PAHs may be absorbed through the lungs, the stomach, or the skin. The extent of absorption varies in both humans and animals with the individual compound and is influenced by vehicle. For instance, oral absorption increases with more lipophilic PAHs or in the presence of oils in the intestinal tract. After inhalation, oral, or dermal exposure of animals, the highest levels of PAHs were found in highly perfused tissues, such as the lung, liver, gastrointestinal tract, and kidney. Animal

studies also show that PAHs cross the placenta. PAHs are rapidly metabolized and excreted in humans and animals. The elimination half-life for benzo[*a*]pyrene in rodents is 20 to 30 hours (ATSDR, 1995).

PAHs have been shown to be metabolized to reactive intermediates by enzyme systems commonly found in the lung, intestines, and liver. These intermediates then covalently bind to cellular macromolecules leading to mutation and tumor development.

5.6.3 Acute Toxicity

There is little data describing the acute toxicity of PAHs after inhalation exposure in humans or animals. Limited information is available on the effects of acute oral and dermal exposure in animals. However, benzo[*a*]pyrene is fatal to mice following ingestion, and the liver and the skin have been identified as target organs in animals after oral or dermal exposure, respectively (ATSDR, 1995). Death has been observed in animals after parenteral exposure to a number of PAHs (ATSDR, 1995). The intraperitoneal LD_{50} values in mice for pyrene, anthracene, and benzo[*a*]pyrene are 514, >430, and 232 mg/kg, respectively.

5.6.4 Chronic Toxicity

Few controlled epidemiological studies have been reported in humans on the effects of exposure to PAHs or to PAH-containing mixtures. However, available information describing chronic-duration dermal exposure of humans to PAHs indicates that PAHs have a high chronic exposure toxicity characterized by chronic dermatitis and hyperkeratosis (ATSDR, 1995). Chronic studies in animals exposed to PAHs by ingestion, intratracheal installation, or skin-painting have not identified adverse health effects other than cancer.

5.6.5 Developmental Toxicity

No information is available regarding the developmental toxicity of PAHs in humans. In vitro studies suggest that human placental endocrine and hormonal function may be adversely affected by exposure to benzo[*a*]pyrene (ATSDR, 1995). Animal data describing developmental effects are mostly limited to benzo[*a*]pyrene administered orally or parenterally and indicate that PAHs have the potential to induce adverse developmental effects such as resorptions and malformations, testicular changes including atrophy of the seminiferous tubules and interstitial cell tumors, immunosuppression, and somatic tumor induction.

5.6.6 Mutagenicity

Benzo[*a*]pyrene has been thoroughly studied in genetic toxicology test systems (ATSDR, 1995). It induces genetic damage in prokaryotes, eukaryotes, and mammalian cells in vitro and produces a wide range of genotoxic effects including gene mutations in somatic cells, chromosome damage in germinal and somatic cells, DNA adduct formation, unscheduled DNA synthesis, sister chromatid

exchange, and neoplastic cell transformation. The genotoxic effects of the other PAHs have been investigated using both in vivo and in vitro assays. All but three of the PAHs (acenaphthene, acenaphthylene, and fluorene) were reported to be mutagenic in at least one in vitro assay with the bacterium *S. typhimurium*.

5.6.7 Carcinogenicity

Evidence indicates that mixtures of PAHs are carcinogenic in humans. This evidence comes primarily from occupational studies of workers exposed to mixtures containing PAHs as a result of their involvement in such processes as coke production, roofing, oil refining, or coal gasification (ATSDR, 1995). Cancer associated with exposure to PAH-containing mixtures in humans occurs predominantly in the lung and skin following inhalation and dermal exposure, respectively. In animals, individual PAHs have been shown to be carcinogenic by the inhalation route (benzo[*a*]pyrene) and the oral route (e.g., benz[*a*]anthracene, benzo[*a*]pyrene, and dibenz[*a,h*]anthracene). Dermal exposure of animals to benz[*a*]anthracene, benzo[*a*]pyrene, benzo[*b*]fluoranthene, benzo[*k*]fluoranthene, chrysene, dibenz[*a,h*]anthracene, or indeno[*1,2,3-cd*]pyrene has been shown to be tumorigenic in mice.

EPA has performed weight-of-evidence evaluations of several PAHs. The carcinogenicity classifications currently verified by EPA's Carcinogenicity Risk Assessment Verification Endeavor Work Group (IRIS, 1994) are listed below:

- Acenaphthylene — D (not classifiable as a human carcinogen)
- Anthracene — D
- Benz[*a*]anthracene — B2 (probable human carcinogen)
- Benzo[*a*]pyrene — B2
- Benzo[*b*]fluoranthene — B2
- Benzo[*k*]fluoranthene — B2
- Benzo[*g,h,i*]perylene — D
- Chrysene — B2
- Dibenz[*a,h*]anthracene — B2
- Fluoranthene — D
- Fluorene — D
- Indeno[*1,2,3-cd*]pyrene — B2
- Phenathrene — D
- Pyrene — D

The EPA and others have developed a relative potency estimate approach for the PAHs (Nisbet and LaGoy, 1992; U.S. EPA, 1993s). Using this approach, the cancer potency of the other carcinogenic PAHs can be estimated based on their relative potency to benzo[*a*]pyrene. Table 5-2 lists the toxicity equivalence factors (based on carcinogenicity) calculated by Nisbet and LaGoy (1992) for PAHs discussed above.

Table 5-2. Toxicity Equivalent Factors for Various PAHs

Compound	Toxicity Equivalency Factor (TEF)
Dibenz[*a,h*]anthracene	5
Benzo[*a*]pyrene	1
Benz[*a*]anthracene	0
Benzo[*b*]fluoranthene	0.1
Benzo[*k*]fluoranthene	0.1
Indeno[*1,2,3-cd*]pyrene	0.1
Anthracene	0.01
Benzo[*g,h,i*]perylene	0.01
Chrysene	0.01
Acenaphthene	0.001
Acenaphthylene	0.001
Fluoranthene	0.001
Fluorene	0.001
Phenathrene	0.001
Pyrene	0.001

Source: Nisbet and LaGoy (1992).

U.S. EPA (1993s) has derived relative potency estimates based on mouse skin carcinogenesis. These are shown in Table 5-3.

5.6.8 Special Susceptibilities

ATSDR has indicated people with nutritional deficiencies, genetic diseases that influence the efficiency of DNA repair, and immunodeficiency due to age or disease may be unusually susceptible to the effect of PAHs (ATSDR, 1995). In addition, people who smoke, people with a history of excessive sun exposure, people with liver and skin diseases, and women, especially of reproductive age, may be at increased risk. Individuals with hepatic metabolizing enzymes that can be induced by PAHs may be unusually susceptible to the toxic effects of PAH exposure by virtue of producing more toxic metabolites. Fetuses may be susceptible to the effects of toxic PAH metabolites produced by maternal exposure, due to increased permeability of the embryonic and fetal blood-brain barrier and the immaturity of the enzymatic systems that are responsible for elimination.

Table 5-3. Relative Potency Estimates for Various PAHs

Compound	Relative Potency[a]
Benzo[*a*]pyrene	1.0
Benz[*a*]anthracene	0.145
Benzo[*b*]fluoranthene	0.167
Benzo[*k*]fluoranthene	0.020
Chrysene	0.0044
Dibenz[*a,h*]anthracene	1.11
Indeno[*1,2,3-cd*]pyrene	0.055[b]

Source: U.S. EPA, 1993s.

[a] Model was $P(d)=1-\exp[-a(1+bd)^2]$ for all but indeno[1,2,3-c,d]pyrene.

[b] Simple mean of relative potencies (0.021 and 0.089); the latter derived using the one-hit model.

5.6.9 Interactive Effects

Because humans are usually exposed to PAHs in complex mixtures rather than to individual PAHs, it is important to understand the potential interactions between the PAHs and other components of the mixture (ATSDR, 1995). Interactions may occur among chemicals in a mixture prior to exposure or may occur after exposure as a result of differing effects of the mixture components on the body. Synergistic and/or antagonistic interactions with regard to the development of health effects, particularly carcinogenesis, may occur. The interaction between noncarcinogenic and carcinogenic PAHs has been extensively examined in animals. Weakly carcinogenic or noncarcinogenic PAHs, including benzo[*e*]pyrene, benzo[*g,h,i*] perylene, fluoranthene, or pyrene exhibit co-carcinogenic potential and tumor-initiating and promoting activity when applied with benzo[*a*]pyrene to the skin of mice. In contrast, benzo[*a*]fluoranthene, benzo[*k*]fluoranthene, chrysene, and a mixture of anthracene, phenathracene, and pyrene have been shown to significantly inhibit benzo[*a*]pyrene-induced sarcoma after injection in mice. Several experiments have indicated that mixtures of several PAHs are less potent with respect to carcinogenicity than the individual PAHs that constitute the mixture.

The majority of human exposure to PAHs occurs in the presence of particles or other environmental pollutants that may influence the toxicity of the PAHs. For instance, inhalation exposure to PAHs in the presence of particulate matter greatly increases respiratory tract tumors in laboratory animals, due to the fact that the particles are cleared more slowly from the lungs, thus allowing the particle-bound PAHs to remain in the respiratory tract for longer periods of time. Similarly, concomitant exposure to asbestos increases bronchopulmonary cancers. Exposure to solvents or other environmental compounds that increase metabolism

of the PAHs may increase or decrease toxicity, depending on whether the individual PAH must be transformed to toxic intermediates in order to exert its adverse effect.

5.6.10 Critical Data Gaps

A joint team of researchers from ATSDR, NTP, and EPA have identified the following data gaps: human responses to acute, intermediate (14 to 365 days), and chronic exposure, subchronic reproductive tests in various species, developmental toxicity studies in two species, immunotoxicity studies of animals and humans, and neurotoxicity studies in humans and animals (ATSDR, 1995).

5.6.11 Summary of EPA Levels of Concern

Carcinogenicity (benzo[*a*]pyrene) 7.3 per mg/kg/d.

5.6.12 Major Sources

ATSDR (1995), IRIS (1997), U.S. EPA (1995).

5.7 POLYCHLORINATED BIPHENYLS (PCBs)

5.7.1 Background

Polychlorinated biphenyls (PCBs) are a mixture of chlorinated biphenyl chemicals comprised of various chlorine substitution patterns. There are 209 possible PCB congeners. Mixtures of PCBs were marketed in the United States under the trade name Aroclor, with a numeric designation that indicated their chlorine content. Although production and use were banned in 1979, the chemical group is extremely persistent in the environment and bioaccumulates through the food chain. There is evidence that some dioxin-like PCB congeners, which are assumed to be the most toxic, preferentially accumulated in higher organisms. Consequently, the aggregate toxicity of a PCB mixture may increase as it moves up the food chain (U.S. EPA, 1993a). As a result of this, the congeneric composition of PCB mixtures found in fish tissue may differ significantly from the environmental PCB source. Often the mixtures of interest are not those that have been used in studies of laboratory animals to determine toxicity. The preferable studies, under these conditions, are those that utilize human dose-response data from populations who have consumed PCBs via fish or who have been exposed to PCBs in occupational settings. When reliable human data are lacking, animal data may need to be used.

PCB exposure is associated with a wide array of adverse health effects in experimental animals, but the effects of PCB exposure in humans are less clear. Many effects have only recently been investigated (e.g., endocrine effects), and the implications of newer studies are not fully known. The health effects of PCBs are still under active evaluation and currently there is not sufficient information on the specific congeners to develop congener-specific quantitative estimates of health risk (ATSDR, 1995; U.S. EPA, 1993a). Due to the lack of congener-specific information, the Office of Water recommends, as an interim measure, that total PCB concentrations be reported as the sum of Aroclors. The first volume in this document series, *Sampling and Analysis*, contains a detailed discussion of analysis of this group of chemicals (U.S. EPA, 19953a).

5.7.2 Pharmacokinetics

PCBs are absorbed through the GI tract and distributed throughout the body. Studies of individual chlorobiphenyl congeners indicate, in general, that PCBs are readily absorbed, with oral absorption efficiency of 75 to greater than 90 percent in rats, mice, and monkeys (IRIS, 1997). Due to their lipophilic nature, PCBs, especially the highly chlorinated congeners, tend to accumulate in lipid-rich tissues. Greater relative amounts of PCBs are usually found in the liver, adipose, skin, and breast milk. Human milk may contain a large amount of PCBs due to their high fat content (ATSDR, 1995). A Canadian study found human milk concentrations more than 10 times higher than whole blood concentrations. This is important because it has been shown that absorption of penta-, hexa-, and heptachlorobiphenyls from breast milk by nursing infants may reach over 90 percent of the dose (ATSDR 1995). It has been estimated that, in some

industrialized countries, an infant may accumulate 6.8 percent of its lifetime PCB body burden during an exclusive nursing period of 6 months (Kimbrough, 1995). The PCB congener composition of milk differs from that of the PCB source. Offspring can also be exposed to PCBs through placental transfer. PCBs have also been measured in other body fluids including plasma, follicular fluid, and sperm fluid. Indirect evidence of oral absorption in humans is available from studies of subjects who consumed PCB-contaminated fish and PCB-contaminated rice oil, from a volunteer who ingested a PCB mixture, and from nursing infants (ATSDR, 1995). Pharmacokinetics data do not suggest route-specific target organs.

The retention of PCBs in fatty tissues is linked to the degree of chlorination and also to the position of the chlorine atoms in the biphenyl ring. In general, higher chlorinated PCBs persist for longer periods of time. Studies indicate that the metabolism of PCBs by monkeys and rats is more similar to humans than other species tested (IRIS, 1997). Pharmacokinetics modeling of PCB disposition indicates that PCB movement in the body is a dynamic process, with exchanges between various tissues that depend on fluctuating exposure levels to specific congeners. The result is clearance of congeners that are more easily metabolized and retention of those that resist metabolism (ATSDR, 1995).

There are some data on the half-life of the various PCBs in humans. In a volunteer who ingested a PCB mixture containing 54 percent chlorine, the elimination half-lives from blood for two hexachlorobiphenyls and one heptachlorobiphenyl congener ranged from 121 to 338 days (ATSDR, 1995). In occupationally exposed individuals, lower chlorinated congeners had half-lives between 1 and 6 years, whereas higher chlorinated PCBs had half-lives ranging from 8 to 24 years (ATSDR, 1995). In subjects who consumed PCB-contaminated rice in Taiwan, the half-lives for several pentachlorobiphenyls ranged from 3 to 24 months.

PCBs induce mixed function oxidases and different congeners induce specific forms (isozymes) of the cytochrome P-450 system. Although there has been much research into the mechanisms of PCB toxicity, there has not been clear definition of the mechanisms for most congeners. The congeners appear to act by a variety of mechanisms (ATSDR, 1995). A few highly potent PCB congeners (dioxin-like congeners) bind to a cytosolic protein, the Ah receptor, which regulates the synthesis of a variety of proteins. The toxicity of these congeners is related to steps that follow the initial binding with the Ah receptor. The toxicity of other PCB congeners seems to be unrelated to the Ah receptor. Ultimately, the toxicity of a PCB mixture may depend on the toxicity of the individual congeners and their interactions. A detailed discussion of PCB pharmacokinetics is available in the ATSDR Toxicological Profile for PCBs (ATSDR, 1995).

5.7.3 Acute Toxicity

Studies in animals have shown that exposure to very high PCB doses can cause death. However, doses of such magnitude are unlikely in environmental exposures and current industrial settings. There have been no reports of deaths in humans

after exposure to PCBs (ATSDR, 1995). Immature animals appear to be more sensitive to acute lethal effects of PCBs than adults (ATSDR, 1995).

5.7.4 Chronic Toxicity

Numerous effects have been documented in studies in animals including hepatic, gastrointestinal, hematological, dermal, body weight, endocrine, immunological, neurological, reproductive, developmental, and liver cancer (ATSDR, 1995). Most of the studies have involved oral exposure. Despite the variety of adverse effects observed in animals exposed to PCBs, frank adverse effects in humans have not been observed. This has been attributed to the fact that, in most cases, the dosages tested in animals were considerably higher than those found in occupational exposures (James et al.,1993; Kimbrough, 1995). There is also some evidence suggesting that monkeys may be much more sensitive than humans.

EPA has derived an RfD of 2×10^{-5} mg/kg/d for Aroclor 1254 (IRIS, 1997). The RfD was based on a LOAEL of 0.005 mg/kg/d for ocular and immunological effects in monkeys. The study reported ocular exudate and inflamed Meibomian glands in the monkeys, as well as significant reductions in antibody levels (IgM and IgG) in response to injected sheep red blood cells at the lowest dose tested after chronic treatment with Aroclor 1254. Uncertainty factors of 10 for sensitive individuals, 3 for extrapolation from monkeys to humans, 3 for extrapolation from a subchronic exposure to a chronic RfD, and 3 for use of a minimal LOAEL were applied, resulting in a total uncertainty factor of 300. This RfD is used to calculate the consumption limits for noncarcinogenic effects for the general population listed in Section 4.

EPA has medium confidence in the study used as the basis for the RfD, in the database, and in the RfD. EPA based this rating on the fact that the database consisted of a large number of laboratory animal and human studies; however, there were some inconsistencies in the effect levels for reproductive toxicity and the results of an unpublished study were considered (IRIS, 1997).

ATSDR has determined that immunological effects are a sensitive endpoint for chronic toxicity and developed an MRL of 2×10^{-5} mg/kg/d based on such effects (ATSDR, 1995). The studies used as the basis for the MRL are the same as those listed above in the IRIS discussion. Uncertainty factors of 10 each for the use of a LOAEL and for human variability were used. A factor of 3 was used for extrapolation from animals to humans. Decreased IgG and IgM levels were noted. Chronic toxicity in other organ systems (as listed above) was noted at exposure levels higher than the LOAEL of 0.005 mg/kg/d (ATSDR, 1995).

5.7.5 Developmental Toxicity

PCB mixtures have been shown to cause adverse developmental effects in experimental animals (ATSDR, 1995). Several studies in humans have also suggested that PCB exposure may cause adverse effects in children and in developing fetuses (U.S. EPA, 1995). However, study limitations, including lack of

control for confounding variables, and deficiencies in the general areas of exposure assessment, selection of exposed and control subjects, and the comparability of exposed and control samples have obscured the interpretation of the results (ATSDR, 1995).

The RfD for Aroclor 1016 is based on adverse developmental effects observed in monkeys in a 22-month study (discussed below under longer-term developmental studies). This study established a NOAEL of 0.007 mg/kg/d. Applying an uncertainty factor of 100 (3 for sensitive individuals [infants exposed trans-placentally], 3 for interspecies extrapolation, 3 for database limitations [male reproductive effects are not directly addressed in studies and two-generation reproductive studies are not available], and 3 for extrapolation from subchronic to chronic) to the NOAEL yields an RfD of 7×10^{-5} mg/kg/d (IRIS, 1997). However, since the RfD for Aroclor 1254 is more conservative (2×10^{-5} mg/kg/d) and protects against adult toxicity concerns as well as the risk to the fetus and children, this RfD will be used to calculate the consumption limits for all populations (adults, women of reproductive age, and children).

EPA has medium confidence in the study used as the basis for the RfD, in the database, and in the RfD. EPA based this rating on the fact that the critical study was well conducted in a sensitive animal species and the database for PCBs in general is extensive; however, since mixtures of PCBs found in the environment do not match the pattern of congeners found in Aroclor 1016, EPA felt that only a medium confidence ranking could be given. For those particular environmental applications where it is known that Aroclor 1016 is the only form of PCB contamination, EPA stated that the RfD could be considered to have a high confidence rating (IRIS, 1997).

The following discussion of developmental toxicity contains study information in the following order: human data, short-term, intermediate length, and longer-term studies, and a summary.

A study was conducted of pregnancy outcomes in women who had consumed PCB-contaminated fish from Lake Michigan over an average of 16 years (exposure both prior to and during pregnancy). Although exposure quantification was not precise, it has been estimated that the average exposure was 5×10^{-4} mg/kg/d. Contaminated fish consumption and levels of total PCBs in cord serum correlated with lower birth weight, smaller head circumference, and shorter gestational age. However, when the two populations were divided according to the cord serum level, the great majority in the low-level group were fish eaters, which suggested that fish consumption rates were poor indicators of PCB exposure. Fish consumption, however, was correlated with delayed neuromuscular maturity, and, at 7 months, the children had subnormal visual recognition memory. The exposure estimates in this study were not precise and varied widely; the recall ranged over a number of years with a mean consumption duration (as noted above) of 16 years and the PCB concentrations in different types of fish of 168 ppb to 3,012 ppb. Children from this cohort have been examined at age 4 and 11 years. At age 4, cord serum PCB levels were associated with impaired short-term memory. Activity

level was inversely related to 4-year serum PCB level and also to maternal milk PCB level. At age 11, prenatal exposure to PCBs was associated with lower full-scale and verbal IQ scores after controlling for potential confounding variables such as socioeconomic status. Exposure during breast feeding, assessed based on PCB concentrations in milk and the number of weeks of nursing, was not associated with the results of the tests, neither was serum concentration of PCBs at 11 years of age. The results from this series of studies were confounded by the fact that there may have been maternal exposure to other chemicals and the fact that the exposed group, on average, drank more alcohol and caffeine, prior to and during pregnancy, weighed more, and took more cold medications during pregnancy, than the nonexposed group (ATSDR, 1995).

A pharmacokinetics approach to estimating safe exposure levels has been taken by the Great Lakes Sport Fish Advisory Task Force using the Michigan study data (Anderson and Amrhein, 1993). This approach utilized relationships between milk PCB concentrations, fish intake and concentrations, and developmental effects. Assumptions were made regarding body weight (60 kg), percentage of body fat (25 percent), and the biological half-life of PCBs in humans (1 year) (Anderson and Amrhein, 1993). The pharmacokinetics approach has the potential for introducing more precision to the process of estimating thresholds and evaluating dose-response relationships. However, it relies on the use of many physiological variables, as well as dose and response values. In the specific case of the Great Lakes approach, there is concern that the assumptions that were made for the “average” women and “average” body fat composition do not take into consideration the 49 percent of women who have above-average values. Although this variability would introduce minimal alterations at values near the average, there could be significant deviation from predicted values at the 75th or 90th percentiles. The approach also assumes that reproduction occurs at 25 years of age with the estimated body burden based on this assumption (Anderson and Amrhein, 1993). Maternity over the age of 25 would entail greater exposure to the fetus due to the higher maternal body burden associated with a longer accumulation period.

A study of children born to women with background body burdens of PCBs in North Carolina found no correlation between birth weight or head circumference with PCB levels. The authors reported that neurobehavioral deficits observed through 2 years of age were not detectable at ages 3, 4, and 5, based on intellectual and motor function assays. Exposure was confounded by the presence of DDE in blood and milk samples from the mothers, although it was shown that some of the behavioral deficits were more closely associated with PCB exposure. This study utilized PCB body burdens rather than intake as the measure of exposure (ATSDR, 1995).

Four additional relevant studies were summarized by ATSDR (1995). A study of women from the Green Bay, Wisconsin, area found no significant differences between a control group and fish eaters regarding stillbirths, multiple births, congenital anomalies, and low birth weight. Another study of PCB-contaminated Lake Ontario sports fish found no consistent relationship between sports fish

consumption and/or PCB exposure and incidence of spontaneous fetal death. However, since fetal death was the outcome measured, the results could not rule out an effect of PCBs on reproduction. A third study compared a small number of women who had spontaneous preterm delivery and a matched control group and found no association between serum PCB levels and spontaneous preterm birth. The fourth study examined infants born to mothers occupationally exposed to PCBs. Infants born to mothers with high exposure had lower mean birth weight and shorter mean gestational age than those born to low-exposure workers. After adjustment for relevant covariates, it was concluded that the decreased birth weight may have been mediated by exposure to high levels of PCBs. The authors further indicated that the small difference in birth weight had no clinical significance for term infants.

The results of animal studies generally support those observed in humans. Short-term studies in animals exposed prenatally to PCBs have identified the following effects: hydronephrosis in mice after a single dose of 244 mg/kg (Aroclor 1254) on gestation day 9; no effects in mice following 12 daily doses of up to 12.5 mg/kg/d (Aroclor 1254) on gestation days 6 to 18; fetal weight reduction in rats with 9 days of dosing at 5 mg/kg/d with reduced survival at 15 mg/kg/d and a NOAEL of 2.5 mg/kg/d (Aroclor 1254); and impaired learning in rats at 4 mg/kg/d with 10 days of dosing (Fenclor 42). Decreased survival was observed at higher doses. In addition, decreased fertility was observed in male offspring of rats treated with $\geq$8 mg/kg/d (Aroclor 1254) during lactation. Based on the results of short-term exposure assays, ATSDR concluded that neurobehavioral endpoints may be the most sensitive for assessing developmental effects.

Intermediate-length exposure studies (e.g., during the prenatal and lactational periods) indicate neurological, thyroid, liver, growth, and hormonal abnormalities in offspring and reduced litter size (ATSDR, 1995). Delayed growth and 89 percent neonatal death was reported in mink at 0.18 mg/kg/d (Aroclor 1254) and, therefore, this exposure level constitutes an FEL (frank effect level). Fetal death was also observed in monkeys following maternal treatment with 0.1 mg/kg/d Aroclor 1254. Mink and monkeys appear to be more sensitive species for PCB-induced developmental toxicity than rodents (ATSDR, 1995).

Information on chronic developmental toxicity is available from studies in monkeys (ATSDR 1995). Exposure periods ranged from 12 to 37 months. The lowest LOAEL was 0.005 mg/kg/d for inflammation of tarsal glands, nail lesions, and gum recession in offspring of monkeys exposed to Aroclor 1254. Adverse neurobehavioral effects were reported at 0.03 mg/kg/d for Aroclor 1016 and at 0.08 mg/kg/d for Aroclor 1248; the respective NOAELs were 0.007 and 0.03 mg/kg/d. Other effects observed included reduction in birth weight (0.03 to 0.08 mg/kg/d) and increased infant death with doses as low as 0.1 mg/kg/d for Aroclor 1248.

As mentioned above, exposure via lactation is a significant concern for neonates. Animal studies indicate that lactational exposure may be more significant than prenatal exposure. In monkeys, signs of PCB intoxication were observed in

lactationally exposed offspring, but not in offspring exposed only prenatally (ATSDR, 1995).

In summary, the results from some studies in humans suggest that exposure to PCBs may cause developmental effects. However, limitations of these studies diminished the validity of the results.

5.7.6 Mutagenicity

IRIS reports that the majority of mutagenicity assays of PCBs have been negative (IRIS, 1997, for PCB mixtures).

An increase in the percentage of chromosomal aberrations in peripheral lymphocytes was reported in a study of workers manufacturing PCBs for 10 to 25 years. Increased sister-chromatid exchange was also reported in that study. Although workers and controls were matched for smoking and drinking, concurrent exposure to other known human genotoxic chemicals occurred (ATSDR, 1995). A different study found increased incidence of chromatid exchanges in lymphocytes from workers exposed to PCBs in an electric station fire compared to unexposed controls. The possibility that toxic chlorinated dioxins and/or furans generated during the fire may have been responsible for the effects could not be ruled out.

ATSDR reports that most in vitro assays and in vivo animal assays yielded negative results, although both positive and negative results were reported. Positive study results include an increase in unscheduled DNA synthesis (ATSDR, 1995). See also Section 5.7.9.

5.7.7 Carcinogenicity

PCBs are classified by EPA as Group B2; probable human carcinogens . This is based on studies that have found liver tumors in rats exposed to Aroclors 1260, 1254, 1242, and 1016. Recent reevaluation of the animal data showed that PCBs with 60 percent chlorine content consistently induced a high yield of liver tumors in rats and that PCB mixtures with 54 or 42 percent chlorination have a lower carcinogenic potential than those with 60 percent chlorine. Human epidemiological studies of PCBs have not yielded conclusive results (Silberhorn et al.,1990). As with all epidemiological studies, it is very difficult to obtain clear unequivocal results due to the long latency period required for cancer induction and the multiple confounders arising from concurrent exposures, lifestyle differences, and other factors. The currently available human evidence is considered inadequate but suggestive (IRIS, 1997).

The Agency's recent peer-reviewed reassessment published in a final report, *PCBs: Cancer Dose-Response Assessment and Application to Environmental Mixtures* (U.S. EPA, 1996f), adopts an innovative approach that distinguishes among PCB mixtures by using information on environmental processes. It considers all cancer studies (which used commercial mixtures only) to develop a

range of cancer potency factors, then uses information on environmental processes to provide guidance on choosing an appropriate potency factor for representative classes of environmental mixtures and different pathways. Depending on the specific applicaiton, either central estimates or upper bounds can be appropriate. Central estimates describe a typical individual's risk, while upper bounds provide assurance (i.e., 95 percent confidence) that this risk is not likely to be underestimated if the underlying model is correct. Central estimates are used for comparing or ranking environmental hazards, while upper bounds provide information about the precision of the comparison or ranking. In this reassessment, the use of the upper bound values were found to increase cancer potency estimates by only two- or threefold over those using central tendency. Upper bounds are useful for estimating risks or setting exposure-related standards to protect public health and are used by EPA in quantitative cancer risk assessment. Thus, the cancer potency of PCB mixtures is determined using a tiered approach based on environmental exposure routes with upper-bound potency factors (using a body weight ratio to the 3/4 power) ranging from 0.07 (lowest risk and persistence) to 2 (high risk and persistence) per mg/kg/d for average lifetime exposures to PCBs. It is noteworthy that bioaccumulated PCBs appear to be more toxic than commercial PCBs and appear to be more persistent in the body. For exposure through the food chain, risks can be higher than other expsosures.

The high risk and persistence cancer slope factor of 2.0 per mg/kg/d was used to calculate the carcinogenicity fish consumption limits, because the major pathway of exposure to persistent toxic substances such as PCBs is via dietary exposure (i.e., contaminated fish consumption).

5.7.8 Special Susceptibilities

ATSDR has indicated that embryos, fetuses, and neonates are unusually susceptible to PCBs due to their underdeveloped enzymatic systems, which may cause delayed elimination and, therefore, accumulation of PCBs in the body. Breast-fed infants are at particular risk because a steroid secreted in human milk, but not cows' milk, inhibits glucuronyl transferase activity, which is critical to PCB metabolism and excretion (ATSDR, 1995).

Other individuals at potentially greater risk include those with syndromes associated with incompletely developed glucuronide conjugation mechanisms, those with hepatic infections, compromised liver functions, or acute intermittent porphyria (ATSDR, 1995).

In addition, PCBs cause induction of the mixed function oxidase system. Individuals exposed to chemicals (including pharmaceuticals) that rely on the mixed function oxidase system for activation or detoxification may experience altered effectiveness of the chemicals. Further discussion may be found in Appendix C under "Organochlorines."

5.7.9 Interactive Effects

PCBs induce microsomal enzymes. See Appendix C under “Organochlorines” for potential interactions arising from this characteristic.

ATSDR reports that:

> The genotoxicity of numerous carcinogens is potentiated *in vitro* by PCBs, but this does not indicate that PCBs should be regarded universally as tumor promoters because of the protective role of PCBs against carcinogenicity of many genotoxic carcinogens in vivo (ATSDR, 1995).

MIXTOX reports potentiation between PCBs and mMirex in a rat dietary study. Other studies of this combination have not found interactive results (MIXTOX).

5.7.10 Critical Data Gaps

A joint team of scientists from EPA, ATSDR, and NTP have identified the following data gaps: human epidemiological studies; genotoxicity studies of various mixtures of PCBs including cytogenetic analysis of human populations exposed to PCBs; reproduction studies in humans and animals including fertility studies in males of a sensitive species; developmental studies including histological examination of developing neurological tissues in experimental animals, neurodevelopmental studies designed to identify NOAELs, and immunological studies in animals exposed in utero; immunotoxicity studies in humans and animals; neurotoxicity studies in humans with high PCB body burdens and in animals; chronic studies to determine the most sensitive animal target organ and species; human studies on PCBs and hypertension and liver toxicity; pharmacokinetics studies; and studies to elucidate the differing toxicities of the various congeners comprising PCB mixtures; studies to elucidate the mechanisms and significance of Ah-receptor-independent effects (ATSDR, 1995).

5.7.11 Summary of EPA Levels of Concern

Developmental Toxicity	2×10^{-5} mg/kg/d based on Aroclor 1254
Chronic Toxicity	2×10^{-5} mg/kg/d based on Aroclor 1254
Carcinogenicity	2.0 per mg/kg/d based on mixed PCBs.

5.7.12 Major Sources

ATSDR (1995), HSDB (1993), IRIS (1997), James et al. (1993), Kimbrough (1995), Silberhorn et al. (1990), U.S. EPA (1996f).

5.8 DIOXINS

5.8.1 Background

Dioxin has been undergoing extensive review within EPA for several years. Consequently, only a brief summary, taken from Volume 1 of this guidance series (second edition), is provided below. Currently, the EPA's dioxin reassessment document, which includes two reports entitled *Estimating Exposure to Dioxin-like Compounds* (three volumes) (U.S. EPA, 1994a) and *Health Assessment Document for 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) and Related Compounds* (three volumes) (U.S. EPA, 1994b) is undergoing final review. It is anticipated that the dioxin reassessment document will be sent for final external peer review during the summer of 1997. Following peer review, the document will be sent to the Agency's Science Advisory Board for final review by the fall of 1997. The final dioxin reassessment document is scheduled for release in 1998.

Dioxin is a generic term that is used, in this case, to specify 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD). It is recommended that the 17 2,3,7,8- substituted tetra- through octa-chlorinated dibenzo-*p*-dioxins and dibenzofurans be considered together as a simplifying and interim approach until further guidance is available on this chemical group. Alternatively, the reader may consult guidance on the use of a toxicity equivalency approach to refine the toxicity estimate and fish consumption limit calculations (Barnes and Bellin, 1989; U.S. EPA, 1991c).

Dioxin is extremely toxic to humans and animals and affects multiple organ systems. Adverse effects observed in animal studies include teratogenicity, fetotoxicity, reproductive dysfunction, carcinogenicity, and immunotoxicity (U.S. EPA, 1993a). Dioxin has the highest cancer potency in animals of the chemicals evaluated by EPA. A cancer-risk-based health advisory can be calculated using the existing cancer slope factor of $1.56 \times 10^{+5}$ per mg/kg/d (U.S. EPA, 1993a).

5.8.2 Summary of EPA Levels of Concern

Carcinogenicity $1.56 \times 10^{+5}$ per mg/kg/d.

5.8.3 Major Source

U.S. EPA (1993a).